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*Adapted from one of the case reviews in A Therapy for Anxiety Tension Reactions. Mr. A.'s symptoms are typical of the type of patient who has, since childhood, braced himself as if to meet danger. In adulthood, his body has become chronically tense, his mind chronically anxious. The authors have found that Mr. A. and patients like him can be trained to relax, both at work and in their leisure hours. When the new habit of relaxation is formed, the patient's psychic symptoms and his somatic symptoms disappear.

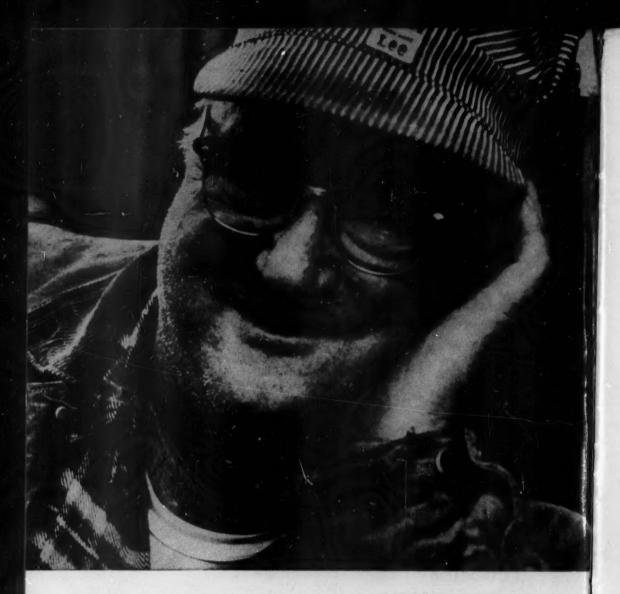
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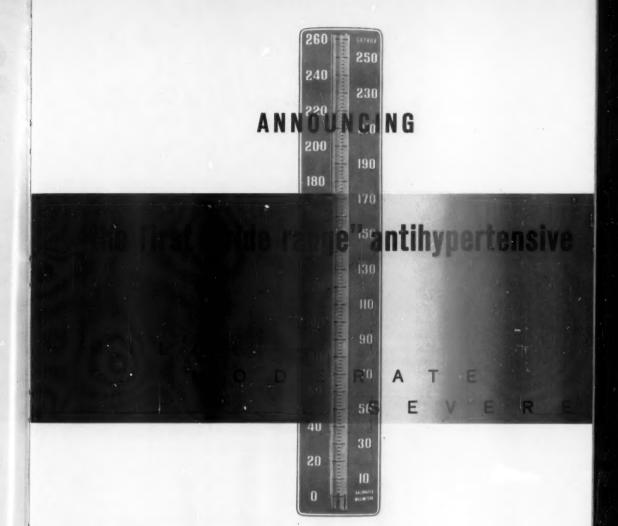
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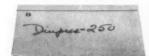
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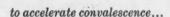
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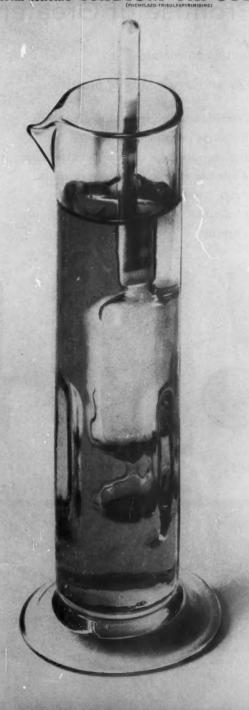


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- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis



Ulcerative Colitis



Radiation Proctitis



Postoperative Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth

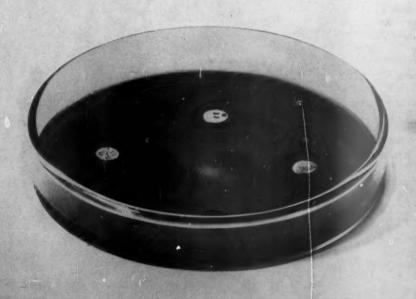


IF URINARY INFECTION PROVES CHRONIC:

Mandelamine is antibacterial, yet is not an antibiotic! Effective in many urinary tract infections resistant to antibiotics and sulfonamides, won't sensitize patients, no resistant strains develop. Mandelamine obviates need for alkalis or forcing of fluids, and it is excellent for long term therapy. Cost is low.



MORRIS PLAINS, N. J.



for all your patients starting on corticoids

Kenacort safely starts your patients off right - with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased antiallergic, antirheumatic or anti-inflammatory activity is provided on a low dosage schedule.1-3 Clinical improvement is accomplished without water or salt retention, 1-4 or adverse effect on blood pressure. 2-3,5 A low sodium diet is not necessary.4,5 Gastrointestinal disturbances are negligible^{2,4,5} with less chance of peptic ulcer.4 and there is no psychic stimulation to distort the clinical response.1-3 This makes Kenacort particularly valuable in treating your "problem patients" - such as the obese or hypertensive and the emotionally disturbed.

- 1. Freyberg, R.H.: Berntsen, C.A., fr., and Heliman, L.: Arth. & Rheum. 1:215 (June) 1958.
 2. Sherwood, H., and Cooke, R.A.: J. Aliergy 28:97 (March) 1957.
 3. Shelley, W. S.; Harun, J.S., and Pilisbury, D.M.: J.A.M.A. 187:959 (June 21) 1958.
 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1956.
 5. Harlung, E.F.: J.A.M.A. 187:973 (June 21) 1956.

Squib Triemcinolone

for all your arthritic patients requiring corticoids

Kenacort, particularly in the treatment of your arthritic patients, has proved effective where other steroids have failed. It provides prompt, safe relief of pain, stiffness and swelling - and may even forestall crippling deformities if started soon enough. Rapid clinical improvement is obtained on a low dosage schedule1-3 with few side effects to worry about.1-5 (Kenacort is particularly valuable for your arthritic patients with hypertension, cardiac disease, obesity 'and those prone to psychic disturbances.) And clinical evidence has shown that Kenacort suppresses the rheumatic process.1,5 Because of its relative freedom from untoward reactions, it provides corticosteroid benefits to many patients who until now have been difficult to control. Kenacort, too, offers the same benefits when treating allergies, dermatoses, and asthma.

SUPPLIE

Scored tablets of 1 mg. — Bottles of 56 Scored tablets of 2 mg. — Bottles of 50 Scored tablets of 4 mg. — Bottles of 30 and 100

FEWER ANGINAL ATTACKS.
PROTECTS AGAINST PAIN
AND CONTROLS ANXIETY.
(EQUANIL AND PETN)

EQUANITRATE

Meprobamate and Pentaerythritol Tetranitrate

Tablets, vials of 50, meprobamate (200 mg.) and pentaerythritol tetranitrate (10 mg.)

*Teadomark

Whieth



"... Well, I usually prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients like its taste better."

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel.

Suspension: Bottles of 12 fluidounces

Tablets: 0.4 Gram, Bottles of 100

Samples on request

WILLIAM H. ROBER, INC., Philadelphia 44, Pennsylvania





in the patient:

95% effective in published cases1-0

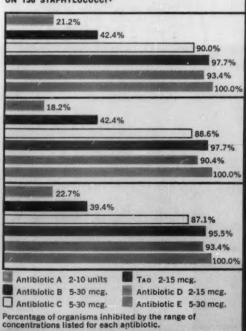
Conditions treated	No. of Patients	/ Cured	Improved	Failure
ALL INFECTIONS	558	448	80	30
Respiratory infections	258	208	31	19
Pharyngitis and/or tonsillitis	65	58	5	2
Pneumonia	90	66	17	7
Infectious asthma	44	38	NEW ATTENDRE	6
Otitis media	31	29	2	
Other respiratory (bronchitis, bronchiolitis, bronchiectasis, pneumonitis, laryngotracheitis, strep throat)	28	17	17	
Skin and soft tissue infections	230	191	38	4
Infected wounds, incisions and		0		
lacerations	41		8	
Abscesses Furunculosis	51			- T
Acne, pustular	58	51	6	ASSES DE
Pyoderma Pyoderma	43 19		15	
Other skin and soft tissue	18	15		
(infected burns, cellulitis, impetigo, ulcers, others)	18			
Genitourinary Infections	28	19	3 4 1 4	250 0.5
Acute pyelitis and cystitis	10		2	
Urethritis with gonorrhea or cystitis	8			
Pyelonephritis	4			3
Salpingitis	5		1	3
Pelvic inflammation with endometriosis	. 1			
Miscellaneous (adenitis, enteritis, enterocolitis, subacute bacterial endocarditis, fever,	42			
hematoma, staphylococcus carriers, osteomyelitis, tenosynovitis, septic arthritis, acute bursitis, periarthritis)				

in the

over 90% effective against resistant staph

laboratory:

COMPARATIVE TESTS BY THREE METHODS (DISC, TUBE DILUTION, CYLINDER PLATE) ON 130 STAPHYLOCOCCI®



Other Tao advantages:

Rapidly absorbed - stable in gastric acid, TAO needs no retarding protective coating

Low in toxicity – freedom from side effects in 96% of patients treated; cessation of therapy is rarely required

Highly palatable — "practically tasteless" active ingredient in a pleasant cherry-flavored medium.

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children-8 months to 8 years, a daily dose of approximately 30 mg./kg.body weight in divided doses has been found effective. Since TAO is therapeutically stable in gastric acid, it may be administered without regard to meals.

Supplied: TAO Capsules - 250 mg. and 125 mg, bottles of 60. TAO for Oral Suspension - 1.5 Gm., 125 mg. per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. Koch, R., and Asay, L. D.: J. Pediat, in press. 2. Leming, B. H., Jr., et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 3. Meliman, et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 4. Olansky, S., and McCormick, G. E., T., Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 5. Shubin, H., et al.: Antibiotics Annual 1957-1958, New York, N. Y., Medical Encyclopedia, Inc., 1958, p. 679. 6. Isenberg, H., and Karc.itz, S.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy 5:527 (Aug.) 1958. 8. Kaplan, M. A., and Goldin, M.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 9. Truent, J. P.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958.

Tao dosage forms — for specific clinical situations

Tao Pediatric Drops

For children - flavorful, easy to administer.

Supplied: When reconstituted, 100 mg. per cc. Special calibrated droppers - 5 drops (approx. 25 mg. of TAO) and 10 drops (approx. 25 mg. of TAO). 10 cc. bottle.

Tao-AC (Tao analgesie, antihistaminic compound)

To eradicate pain and physical discomfort in respiratory disorders.

Supplied: In bottles of 36 capsules.

TAOMID® (TAO with triple sulfas)

For dual control of Gram-positive and Gram-negative infections.

Supplied: Tablets, bottles of 60. Oral Suspension, bottles of 60 cc.

Intramuscular or Intravenous

For direct action—In clinical emergencies.

Supplied: In 10 cc. vials.

WANTED STATE



New York 17, N.Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being

Winthrop Laboratories introduces the first true "TRANQUILAXANT"*

Imcop

a completely new major chemical contribution to therapeutics ... unrelated to any other drug in current use

- . Both a muscle relaxant and a calmative agent.
- . In musculoskeletal disorders, 91 per cent effective.
- In anxiety and tension states, 93 per cent effective.
- · Lower incidence of side effects than with zoxazolamine. methocarbamol or meprobamate.
- . No known contraindications. Blood pressure, pulse rate, respiration and digestive processes unaffected by therapeutic dosage. No effect on hematopoietic system or liver and kidney function.
- · Low toxicity. In animals, even less toxic than aspirin.
- · No gastric irritation. Can be taken before meals.
- · No clouding of consciousness, no euphoria or depression.
- · No perceptible soporific effect, even in high dosage.

designed to be equally effective as both

- a MUSCLE RELAXANT
- a TRANQUILIZER

*tran-qui-lax-ant (tran'kwi-lak'sant) [L. tranquillus, quiet; L. laxare, to loosen, as the muscles]



DOSAGE: One Caplet (100 mg.) orally three or four time daily Relief of symptoms oc and tasts from four to six ho ms occurs in fifteen to thirty minutes

SUPPLIED: Trancopal Caplets® (scored) 100 mg., bot-

Winthrop Laboratories, N. Y. 18, N. Y.

Until the discovery of DECADRON® by MERCK SHARP & DOHME, when your diabetic patients were also in need of corticosteroids, you were often faced with a difficult therapeutic dilemma. Diabetes mellitus was a recognized contraindication to the use of corticosteroids, since they not only aggravated the existing diabetic symptoms, but often precipitated latent diabetes.

NOW EVEN many diabetic patients may have THE FULL BENEFITS OF CORTICOSTEROID THERAPY

DECADRON—the new and most potent of all anti-inflammatory corticosteroids—is remarkable for its virtual absence of diabetogenic effect in therapeutic doses.



to treat <u>more</u> patients <u>more</u> effectively In clinical trials with some 1,500 patients, glycosuria was noted in only two, transitory glycosuria in another two, and flattening of the glucose tolerance curve in one. There were no instances of aggravation of existing diabetes, no increase in insulin requirements. Patients whose diabetes was severely aggravated on prednisolone showed good tolerance when transferred to DECADRON.

to DECADRON.

MORE patients can be treated with DECADRON than with other corticosteroids, because in addition to being practically free of diabetogenic activity, therapy with DECADRON is also practically free of sodium retention, potassium depletion, hypertension, edema and psychic disturbances. Cushingoid effects are fewer and milder. DECADRON has not caused any new or "peculiar" reactions, and has produced neither euphorla nor depression, but helps restore a "natural" sense of well-being.

"natural" sense of well-being.

*DECADRON is a trademark of Merck & Co., Inc.,

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DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA,



"Much betterthank you, doctor"

Proven in research

- 1. Highest tetracycline serum levels
- 2. Most consistently elevated serum levels
- 3. Safe, physiologic potentiation (with a natural human metabolite)

And now in practice

- 4. More rapid clinical response
- 5. Unexcelled toleration

COSA-TETRACYN

GLUCOSAMINE-POTENTIATED TETRACYCLINE

CAPSULES

(black and white) 250 mg., 125 mg. (for pediatric or long-term therapy)

ORAL SUSPENSION

(orange-flavored) 125 mg. per tsp. (5 cc.) 2 oz. bottle

NEW! PEDIATRIC DROPS

(orange-flavored) 5 mg. per drop, calibrated dropper, 10 cc. bottle

COSA-TETRASTATIN*

glucosamine-potentiated tetracycline with nystatin

Antibacterial plus added protection against monilial super-infection

CAPSULES (black and pink) 250 mg. Cosa-Tetracyn (with 250,000 u. nystatin)

ORAL SUSPENSION 125 mg. per tsp. (5 cc.) Cosa-Tetracyn (with 125,000 u. nystatin), 2 oz. bottle

COSA-TETRACYDIN*

glucosamine-potentiated tetracycline-analgesic-antihistamine compound

For relief of symptoms and malaise of the common cold and prevention of secondary complications

CAPSULES (black and orange) - each capsule contains: Cosa-Tetracyn 125 mg.; phenacetin 120 mg.; caffeine 30 mg.; salicylamide 150 mg.; buclizine HCl 15 mg.

REFERENCES: 1. Carlozzi, M.: Antibiotic Med. & Clin. Therapy 5:146 (Feb.) 1958. 2. Welch, H.; Wright, W. W., and Staffa, A. W.: Antibiotic Med. & Clin. Therapy 5:52 (Jan.) 1958. 3. Marlow, A. A., and Bartlett, G. R.: Glucosamine and leukemia, Proc. Soc. Exp. Biol. & Med. 84:41, 1953. 4. Shalowitz, M.: Clin. Rev. 1:25 (April) 1958. 5. Nathan, L. A.: Arch. Pediat. 75:251 (June) 1958. 6. Cornbleet, T.; Chesrow, E., and Barsky, S.: Antibiotic Med. & Clin. Therapy 5:328 (May) 1958. 7. Stone, M. L.; Sedlis, A., Bamford, J., and Bradley, W.: Antibiotic Med. & Clin. Therapy 5:322 (May) 1958. 8. Harris, H.: Clin. Rev. 1:15 (July) 1958.



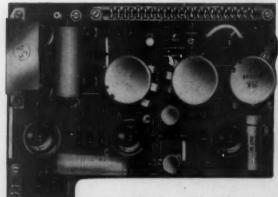
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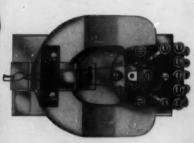
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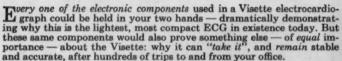
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They've put cardiography on the rod









As you looked at these examples of completely modern electronics used in the Visette, you would see numerous transistors—rugged, miniature, solid devices which do many of the jobs vacuum tubes do, but with the advantages of much greater durability, preferable electrical characteristics in certain applications, and an extremely long operating life. You'd also see wiring which was printed on thin, tough phenolic panels—in place of hundreds of separate pieces of wire; such connections, of course, can't shake loose under constant jarring—and they also make possible "building block" circuitry in the Visette with separate, easily accessible plug-in panels.

And similar advantages in greater ruggedness, longer life, better performance or smaller size would be found in other Visette elements. Each one was chosen for the contribution it could make in achieving a smaller, lighter, more rugged ECG—without sacrificing accuracy. Together, they become part of an electrocardiograph offering unequalled operating convenience and portability. More than 3000 doctors today know this from their own experience—in using a Visette in their own practices.

Descriptive literature, "Questions and Answers" on the Visette in handy folder form, or details of the Sanborn 15-day Test-and-Return Plan available on request. Address "Inquiry Director."



MEDICAL DIVISION 175 Wyman Street, Waltham 54, Massachusetts



Model 300 Visette electrocardiograph, \$625 delivered, continental U. S. A.

NEW 2-PART PLAN FOR TREATMENT OF HYPERTENSION

First

for response within first 24 hours, start patients on

Harmonyl-N

The synergistic action of HARMONYL and NEMBUTAL produces, usually within the first 24 hours, a definite subjective response, so that patients enjoy calmer days, more restful nights while high blood pressure begins to fall. Each HARMONYL-N Filmtab combines 0.25 mg. of HARMONYL, Abbott's alkaloid of Rauwolfia canescens, with 30 mg. of NEMBUTAL Calcium . . . a standard in barbiturate therapy. Suggested dosage is 2 or 3 Filmtabs daily.

"Filmtab-Film-scaled tablets, Abbatt; put. applied for

THER, AFTER TWO TO FOUR WEEKS, WHEN RESPONSE IS ESTABLISHED ...



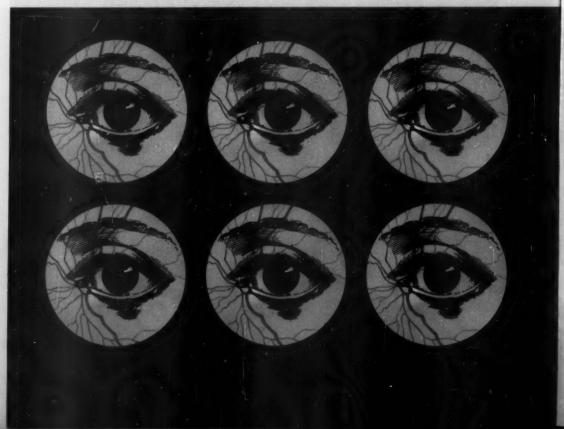
NEW 2-PART PLAN FOR TREATMENT OF HYPERTENSION

Second maintain improved blood pressure levels by switching patients to Harmonyl

When initial tension is overcome and NEMBUTAL's sedation is no longer needed, regular HARMONYL will continue to keep blood pressure at desirable levels... yet won't hamper patients with an excess of side effects. Clinical tests have shown that HARMONYL produces significantly less daytime lethargy than reserpine or the alseroxylon fraction, while controlling blood pressure just as efficiently. Thus, if patients continue to work while under your care, they can work capably. HARMONYL is supplied as 0.1-mg., 0.25-mg. (grooved) and 1-mg. (grooved) tablets. Suggested dosage is 0.25 mg. once or twice a day.

STREE, ARREST LABORATORIES, MONTH GHIZAGO, MAING

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In peptic ulcer: six aids

to total management

ALUDROX SA is not only an effective anticholinergic, but also an antacid, sedative, demulcent, anticonstipant, and pepsin-inhibitor. Thus, one convenient preparation satisfies six requirements of total peptic-ulcer therapy.

An important new anticholinergic of demonstrated usefulness, ambutonium, is responsible for the potent antisecretory and antimotility properties of ALUDROX SA.

SUSPENSION HEW TABLETS SA*

Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide, and Butabarbital, Wyeth

*Sedative and Anticholinergic

SUPPLIED: SUSPENSION, bottles of 12 fl. oz. TABLETS, bottles of 100. Each teaspoonful (5 cc.) and tablet contains 2.5 mg. of ambutonium and 8 mg. of butabarbital combined with aluminum hydroxide and magnesium hydroxide approximating 1 teaspoonful of aluminum hydroxide gel and

¼ teaspoonful of milk of magnesia. Also available: Tablets Ambutonium Bromide, 10 mg., bottles of 100.



Philadelphia 1, Pa.

Patient J. I.

Duodenal Ulcer

Duodenal PATHIBAMATE

before PATHIBAMATE

PATHIB



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sig: 1 tab. t.1.d. and

2 tabs. at bedtime

... calms tension and controls G. I. trauma

AMATE

Meprobamate with PATHILON® Lederle

CYANAMID COMPANY, PEARL RIVER, NEW YORK



Of course, women like "Premarin"

THERAPY for the menopause syndrome should relieve not only the psychic instability attendant the condition, but the vasomotor instability of estrogen decline as well. Though they would have a hard time explaining it in such medical terms, this is the reason women like "Premarin."

The patient isn't alone in her devotion to this natural estrogen. Doctors, husbands, and family all like what it does for the patient, the wife, and the homemaker.

When, because of the menopause, the psyche needs

nursing — "Premarin" nurses. When hot flushes need suppressing, "Premarin" suppresses. In short, when you want to treat the whole menopause, (and how else is it to be treated?), let your choice be "Premarin," a complete natural estrogen complex.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N.Y. Montreal, Canada

protects against anginal attacks



eases cardiac tension



Dosage: Begin with 1 to 2 yellow CANTRAX "10" tab-lets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

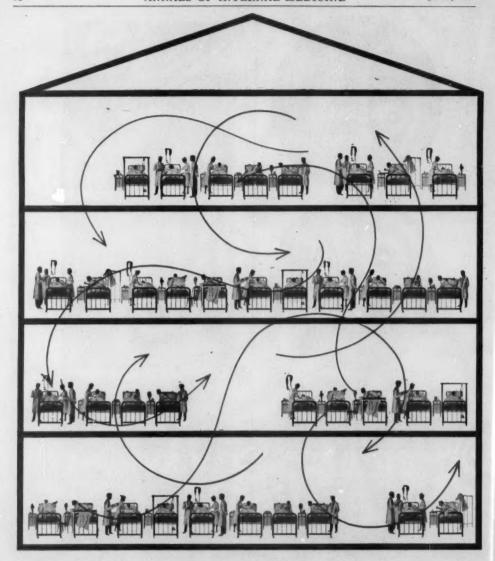
For convenience, write "CARTRAX 10" or "CARTRAX 20."

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. 19:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1968.



New York 17. N. Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being



STOP "HOSPITAL STAPH" WITH **ALBAMYCIN***

RTRADEMARK, REG. U. S. PAT. OFF.— THE UNDOWN BRAND OF CHYSTALLINE NOVOBIOCIN SODIUM TRADEMARK, REG. U. S. PAT. OFF.

Antibiotic-resistant strains of Staphylococcus are meeting their match in Albamycin. Because Albamycin shows no cross resistance with any commonly used antibiotic, it is dramatically effective against unyielding staphylococcal pneumonia or superinfections of pneumococcal pneumonia.

Whether resistant staph is known or suspected, Albamycin is indicated.

ADMINISTRATION AND DOSAGE: The dosage for adults is 500 mg. Albamycin administered intramuscularly or intravenously every 12 hours. As soon as the patient's condition permits, parenteral Albamycin should be replaced with oral Albamycin therapy.

SUPPLIED: Available as 250 mg. capsules; syrup containing 125 mg. Albamycin per 5 cc.; and in the 500 mg. Mix-O-Vial.† The Upjohn Company, Kalamazoo, Michigan



helps reduce blood ammonia levels in hepatic coma

R-gene can reduce blood ammonia levels to shorten the duration of hepatic coma or to prevent impending hepatic coma.

R-gene, a solution of L-arginine, accelerates the conversion in the liver of toxic ammonium to nontoxic urea.

Improvement of the mental status of patients in hepatic coma has been reported to accompany the reduction of

blood ammonia levels usually within 24 to 48 hours following arginine therapy.*

R-gene is indicated in any disease states where elevated

- in hepatic coma or impending hepatic coma
- in ammonia intoxication due to ingestion of ammonium salts
- in acute hepatic insufficiency

ammonia levels exert a toxic effect.

- following massive upper gastrointestinal hemorrhage
- in portal cirrhosis with increased intestinal nitrogenous contents
- in any hepatic encephalopathies with elevated blood ammonia levels

How Supplied: The R-gene package consists of a half liter Saftiflask® containing 400 cc. of a 5% solution of L-arginine, a 100 cc. Ambot® of 50% dextrose, and administration set.

*Najarian, J. S., and Harper, H. A.: Am. J. Med. 21:832 (Dec.) 1956.

Detailed literature is available from your Cutter man or write to Dept. 9-19A

For maximum clinical effective-

ness all measures to reduce am-

monia intake, along with R-gene

administration, should be started including reduction or withdrawal

of protein intake, control of gas-

trointestinal bleeding, prompt re-

moval of blood from the intestine,

large oral doses of neomycin (from 4-12 Gm. daily) to reduce am-

monia production in the intestine.

(The use of dextrose in conjunc-

tion with arginine apparently aids

in the total ammonia utilization.)



CUTTER LABORATORIES

Berkeley, California

Investigator

after investigator reports

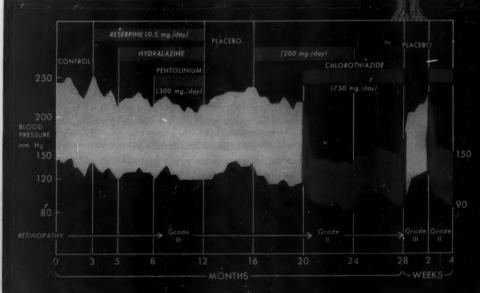
Wilkins, R. W.: New England J. Med. 257:1026, Nov. 21, 1957.

"Chlorothiazide added to other antihypertensive drugs reduced the blood pressure in 19 of 23 hypertensive patients." "All of 11 hypertension subjects in whom splanchnicectomy had been performed had a striking blood pressure response to oral administration of chlorothiazide." "... it is not hypotensive in normotensive patients with congestive heart failure, in whom it is markedly diuretic; it is hypotensive in both compensated and decompensated hypertensive patients (in the former without congestive heart failure, it is not markedly diuretic, ..."

Freis, E. D., Wanko, A., Wilson, I. H. and Parrish, A. E.: J.A.M.A. 166:137, Jan. 11, 1958.

"Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction [16%] of blood pressure." "The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple 'rule of thumb' oral dosage schedules."





In "Chiprothiazide: A New Type of Drug for the Treatment of Arterial Hypertension,"

Hollander, W. and Wilkins, R. W.: Boston Med. Quart. 8: 1, September, 1957.

MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa.



the effectiveness of DIURILE (CHLOROTHIAZIDE)

in

Hypertension

as simple as 1-2-3

- INITIATE THERAPY WITH 'DIURIL'. 'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day.
- ADJUST DOSAGE OF OTHER AGENTS. The dosage of other antihypertensive medication (reserpine, veratrum, hydralazine, etc.) is adjusted as indicated by patient response. If the patient is established on a ganglionic blocking agent (e.g., 'INVERSINE') this should be continued, but the total daily dose should be immediately reduced by as much as 25 to 50 per cent. This will reduce the serious side effects often observed with ganglionic blockade.
- 3 ADJUST DOSAGE OF ALL MEDICATION. The patient must be frequently observed and careful adjustment of all agents should be made to determine optimal maintenance dosage.

SUPPLIED: 250 mg. and 500 mg. scored tablets 'DIURIL' (chlorothiazide); bottles of 100 and 1,000. 'DIURIL' is a trade-mark of Merck & Co., Inc.

Smooth, more trouble-free management of hypertension with 'DIURIL'

FOR PRACTICAL MANAGEMENT OF HYPERTENSION

NEW

A SINGLE PROTOVERATRINE ALKALOID potent...safe...and an important addition to "combination therapy"

The isolation of pure, crystalline protoveratrine A* makes available, for the first time, a single chemically standardized veratrum alkaloid. Now, blood pressure can be lowered with doses smaller than ever before possible in oral veratrum therapy.

In Protalba-R[†] Tablets, protoveratrine A (0.2 mg.) is combined with reserpine (0.08 mg.)—providing two effective hypotensive agents with constant, unvarying potency. In contrast to complex alkaloid mixtures which have uncertain activity, the effects of Protalba-R are predictable and reproducible.

Used alone, Protalba-R can produce a significant decrease in both systolic and diastolic pressure. And, it is the logical supplement to therapy when hypertension cannot be controlled by diet modification and psychogenic measures or the use of tranquilizers and diuretics,

protalba-R

Supplied in bottles of 100 cross-scored tablets.

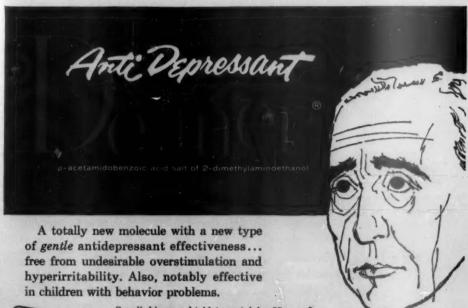
*Patent Pending

†Trademari

PITMAN MOORE COMPANY

In Mild Mild Depression

- · with chronic fatigue
 - · with neurasthenia
 - · with difficulty in concentrating



Northridge, California

Supplied in scored tablets containing 25 mg. of 2-dimethylaminoethanol as the p-acetamidobenzoic acid salt. In bottles of 100 and 500,



"Doctor, I eat like a bird, and I still don't lose weight."

She's wrong, of course. And you know it. She not only eats three meals daily, but she also "snacks" from morning to night. One 'Spansule' capsule, taken in the morning, will curb her appetite all day long, preventing both between-meal nibbling and overeating at mealtimes. Furthermore, 'Dexamyl' provides a mood improvement that encourages patient cooperation and eases adjustment to the low-calorie diet.

DEXAMYL*—for most overweight patients

Tablets . Elixir . Spansule* <u>sustained release</u> capsules

When your overweight patient is listless and lethargic—DEXEDRINE†

*T.M. Reg. U.S. Pat. Off. †T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

MY DAD - HE HURT HIS BACK REAL BAD

"It happened at work while he was putting oil in something"

"He told

felt like it was on

fire"

Mom his shoulder









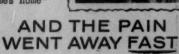


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then you should know...

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1. Bronstein, M.: A.M.A. Arch. Ophth. 57:503, 1957.

2. Soss, T. L.: California Med. 87:266, 1957.

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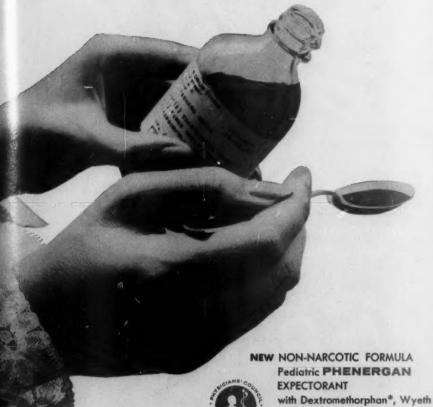
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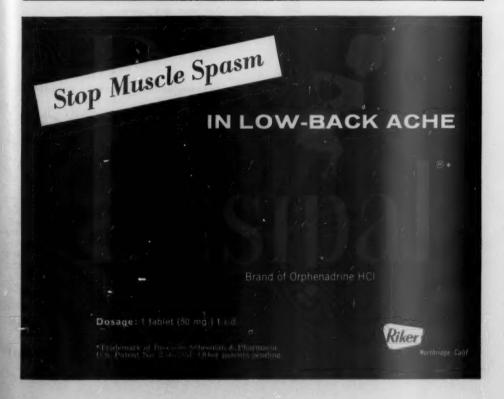
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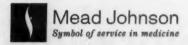


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Celginace provides smooth, nonirritating 'hydrasorbent' bulk in the intestine, not in the stomach. Thus it gives bulk where bulk is needed...and avoids excessive gastric fullness and depression of appetite. And because of superior water absorption and retention, Celginace provides an effective bulk in a dosage of only one to three tablets daily.

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When the patient presents a complex of symptoms, and combined therapy is indicated, Combinace provides (1) smooth, non-irritating, 'hydrasorbent' bulk of alginates, (2) the predictable, yet gentle peristaltic stimulation of Peristim* (3) the moistening action of Colace.

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1. Mutinos, M. G., and Jerzy Glass, G. B.: Gastroenterology 24: 386-389 (May. Aug.) 1983. A workhorse
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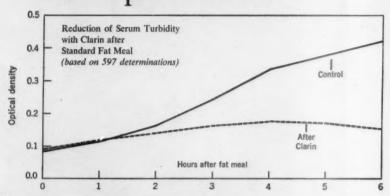


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Clarin

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clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood, 1.2 but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

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Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958.
 Hahn, P. F.: Science 98:19 (July 2) 1943.
 Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
 Rubio, F. A., Jr.: Personal communication.
 Engelberg, H., et al.: Circulation 13:489 (April) 1956.

*Trade Mark. Patent applied for.

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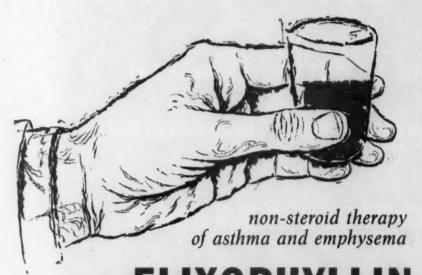
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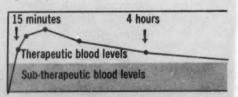


DOSAGE: First two days:

45 cc. (three tbsp.) on arising;

45 cc. (three tbsp.) on retiring;

45 cc. (three tbsp.) once midway between above doses (about 3 P. M.)



After two days of therapy the size of doses should be slightly decreased. Each tablespoonful contains: theophylline 80 mg., alcohol 3 cc. Prescription only—bottles of 16 fl. oz.

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COMPOSITION: Each tablet contains Ilopan (brand of d-panto-thenyl alcohol) 50 mg., choline bitartrate 25 mg.

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DOSAGE: Two tablets three times daily. Three tablets three times daily in severe cases.

HOW SUPPLIED: Bottles of 100 and 500.



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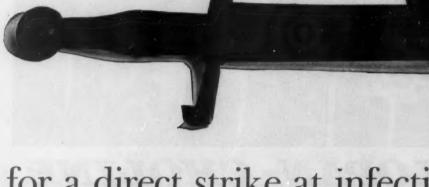
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- a reliable defense against monilial complications

both are often needed when bacterial infection occurs



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It provides a direct strike at all tetracycline-susceptible organisms (most pathogenic bacteria, certain rickettsias, certain large viruses, and Endamoeba histolytica).

It provides the new chemical form of the world's most widely prescribed broad spectrum antibiotic.

It provides unsurpassed initial blood levels—higher and faster than older forms of tetracycline—for the most rapid transport of the antibiotic to the site of infection.

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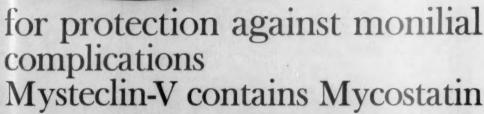
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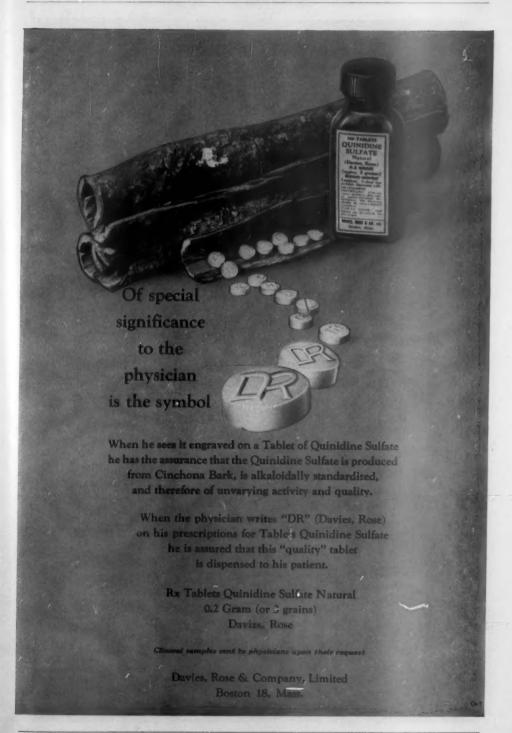
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- 1. Doshay, L. J. et al.: J.A.M.A. 160:348 (Feb.) 1956
- 2. Berris, H.: J.-Lancet 74:245 (July) 1954.

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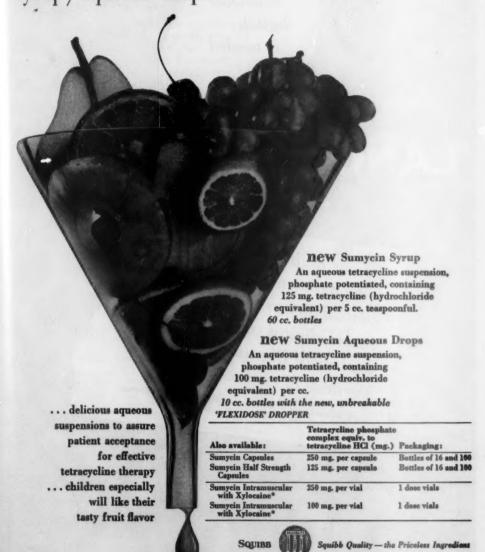


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Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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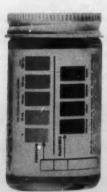
Tests for the detection of protein and glucose.

Source: Free, A. H., and Fonner, D. E: Studies with a combination test for detection of glucose and protein, presented at Division of Biological Chemistry, American Chemical Society, 133rd Nat. Meet., San Francisco, April 13-18, 1958.

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one dip...10 seconds...2 results



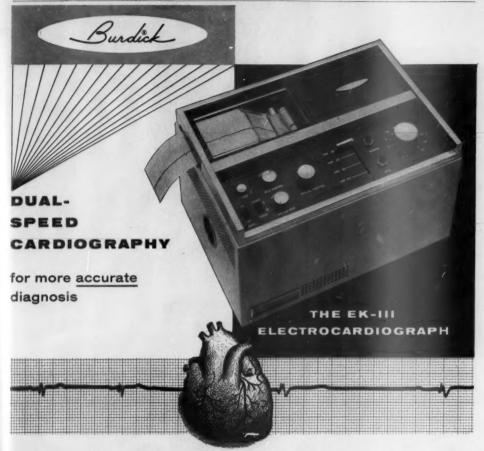
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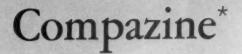
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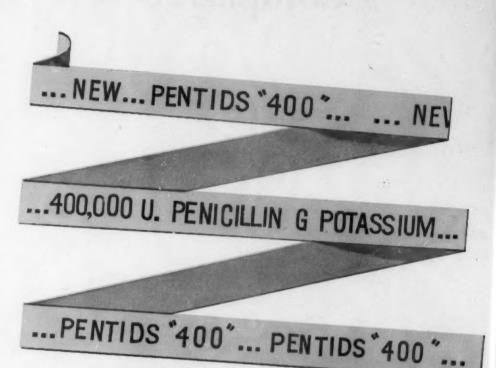
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1. Alexander, L.: Chemotherapy of depression—Use of maprobarnate combined with benactyzine (2-dictiv/seminocitys) benzilate) bydrochloride, J.A.M.A. 166:1019, March 1, 1958.

Composition: Each tablet contains 400 ing, meprobamate and 1 mg. 3-diethylaminoethyl benzilate hydrochleride (benactysine

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References: 1. Alyea, E. P.: Infections and Inflammations of the Male Genital Tract, in Campbell, M.: Urology, Philadelphia, W. B. Saunders Co., 1954, vol. 1, p. 643. 2. Cerroll, G., in panel discussion, J. Am. Geriet. Soc. 5:635, 1957. 3. Barnes, R. W.: Prostatitis, in Conn, F.: Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957, p. 353. 4. Barnes, R. W., in discussion of Chinn, J., and Blachoff, A. J.: Tr. West. Sect. Am. Urol. Acs. 22:189, 1985.

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 Spies, T. D.: <u>J.A.M.A.</u> 167:675 (June 7) 1958.
 Robinson, W. D.: Report to A.M.A. Council on Foods and Nutrition, <u>J.A.M.A.</u> 166:253 (Jan. 18) 1658.

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Lethargy, fatigue and emotional depression secondary to chronic illness in elderly patients; mild depression secondary to short-term illness. (Twenty-three "normal," healthy people also received the drug.)	"For the entire 112 patients 66 per cent showed marked improvements [obvious drug effect and mood improvement]"	"No serious side reactions were noted In no case was it necessary to stop the drug. No evidence of significant effect upon blood pressure or pulse has been found. This is particularly interesting, since these side effects have been common with other mood elevating drugs"2
Drug-induced psychophysiologic depression; physiologic after-effects of certain anesthetics; barbiturate intoxication; moribund states due to systemic infection. (All patients were epileptic, mentally retarded and/or brain damaged.)	"All except two [of 129] patients responded to the initial injection [of parenteral Ritalin] within 1½ to 15 minutes."	"In no instance was there any evidence of untoward effects." " the very poor basic physical condition of our patients in this study, those associated with profound chronic brain damage, accentuates the safety of parenteral Ritalin "8

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REFERENCES: 1. Natenshon, A. L.: Dis. Nerv. System 17:392 (Dec.) 1956. 2. Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey 57:55 (Feb.) 1958. 3. Carter, C. H., and Maley, M. C.: Dis. Nerv. System 18:146 (April) 1957.

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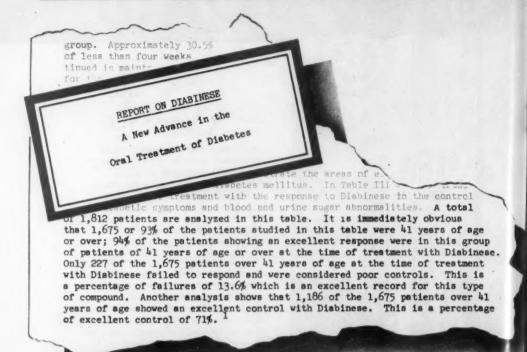
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Peiser² states that even extremely strong convulsive abdominal pain and violent vomiting could be eliminated or substantially improved, and no unpleasant side effects or toxic reactions were noted at any time.

1. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.

2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.

3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.



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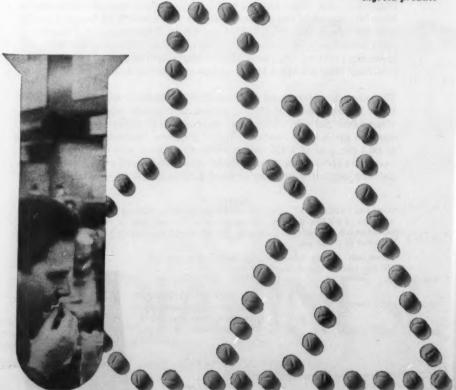
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SUPPLIED—Gitaligin TABLETS 0.5 mg., bottles of 30 and 100.

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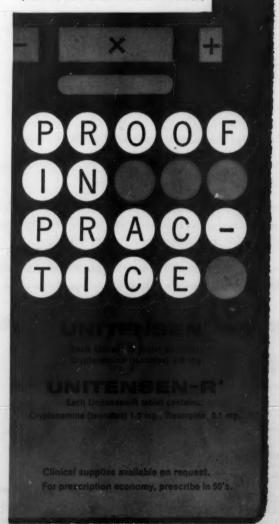
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SUMMARY OF REPORTS

No. of Patients	Results	Percent	
6,553	Excellent	31.0%	
10,843	Good	51.3%	
2,703	Fair	12.8%	
1,033	Unsatisfactory	4.9%	

(Total Number of Side Effects: 638 [3.0%])



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This data deals with the results obtained by 1,988 physicians, treating 21,128 hypertensive patients with Unitensen. The "Proof In Practice" study validates, in day-to-day private practice, the findings of clinical trials conducted in hospitals and institutions. It proves that Unitensen affords safe. dependable office management for the majority of hypertensive patients. Unitensen lowers blood pressure . . . improves cerebral and renal blood flow... exerts no adverse effects on circulation . . . and, is virtually free of side effects.



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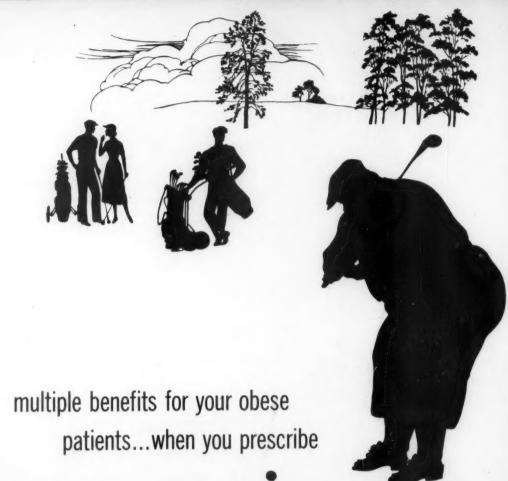
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In a typical study of 1,776 patients¹ treated with Butazolidin for rheumatoid arthritis, osteo-arthritis, ankylosing spondylitis or miscellaneous musculoskeletal disorders, the over-all picture was gratifying. Over 80% of the patients responded favorably. In the more acute cases, results were frequently outstanding. Pain relief was generally accompanied by reduction in joint swelling and increase in mobility. Only 3 patients developed serious reactions.

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(1) McMahon, M. F.: Rheumatism 13:17, 1957. (2) Robins, H. M.; Lockie, L. M.; Narcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. & Digest Treat. 8:1758, 1957. (3) Stein, I. D.: Circulation 12:833, 1955. Complete bibliography furnished on request.

BUTAZOLIDIN® (phenylbutazone Geigy): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN (phenylbutazone Geigy) 100 mg.; aluminum hydroxide 100 mg.; magnesium trisilicate 150 mg.; homotropine methylbromide 1.25 mg.



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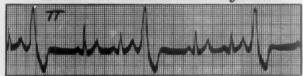
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"While complaints of depression, weakness and fatigue are generally associated with a [severely] restricted caloric regimen, by contrast, patients in this study were cheerful, alert and energetic."4"

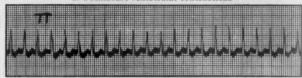
(1) Council on Pharmacy and Chemistry, New and Nonothcial Remedies, J.A.M.A. 163:35(Feb. 2): 1957. (2) Martel, A. Canad, M.A.J. 76:117, 1957. (3) Ressigt, C. J.A.M.A. 165:135 (Sept.714):1957. (4) Natienshon, A. L. Am. Pract. & Digest Treat. 7:1455, 1956
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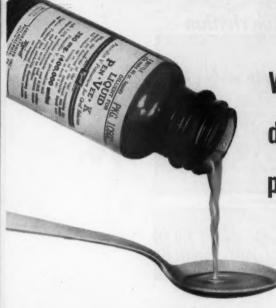
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References: 1. Burrell, Z. I., et al.: Am. J. Cardiol, 1:624 (May) 1958. 2. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:451 (Dec.) 1956.

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Moreover, several investigators report that side effects induced by previous corticosteroid ther-

apy such as gastric intolerance, peripheral edema, headache, vertigo, muscle weakness, ecchymoses, flushing, sweating, moon facies, hypertension, hirsutism and acne often disappeared during therapy with DECADRON.

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Detailed information on dosage and precautions is available to physicians on request.

Supplied: As 0.75 and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100.

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ANNALS OF INTERNAL MEDICINE

VOLUME 50

JANUARY, 1959

NUMBER 1

NEW DRUGS FOR THE TREATMENT OF HYPERTENSION*

By ROBERT W. WILKINS, M.D., F.A.C.P., Boston, Massachusetts

INTRODUCTION

SINCE 1950 a number of new antihypertensive drugs have come into use and have helped to change not only our clinical management but also our basic concepts of essential hypertension. These drugs have in common only their antihypertensive property, and even this is mediated differently by each of them. Thus the ganglionic blocking drugs reduce the activity of the sympathetic nervous system, the veratrum products stimulate the depressor activity of the parasympathetic nervous system, the Rauwolfia derivatives lessen the pressor effects of central nervous agitation, hydralazine dilates the arteriolar system, particularly in the kidney, and chlorothiazide augments natruresis, and may decrease renal pressor activity. Each of these drugs has a place in the treatment of different patients, and several or even all of them may be used in combination in certain cases. The purpose of this paper is to give a resumé of the present status of these new agents, not only as to their beneficial actions but also as to their undesirable side-effects, and to draw some inferences concerning the physiologic mechanisms that may be operating in arterial hypertension.

THE DRUGS

Rauwolfia (table 1), the mildest of the antihypertensive drugs, has definite central nervous sedative or "tranquilizing" effects. These are thought

* Presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 29, 1958.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

Requests for reprints should be addressed to Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine, Boston, Massachusetts.

possibly to be related to the depleting effect of reserpine upon the brain's content of serotonin, the catecholamines, or both. This depleting effect of reserpine might account for the well established clinical observation that, on long-term continued use, the doses of Rauwolfia that can be tolerated without serious mental depression may have to be reduced to a quarter or less of the initial dosage, and often to as little as 0.1 mg. of reserpine a day.

TABLE 1

Drugs for Hypertension Rauwolfia (Reserpine)

- 1. Sedative, "tranquilizer"
- 2. Mildly hypotensive
- 3. Depletes serotonin
- 4. Causes bradycardia 5. Causes nasal stuffiness
- 6. Increases gastrointestinal activity
- 7. Average daily doses: crude root, 100 mg.; alseroxylon, 8 mg.; reserpine, 0.4 mg.

Rauwolfia's main usefulness for long-term treatment is as a preparatory, adjunctive agent to be given should there be need for stronger antihypertensive drugs, such as hydralazine. Because Rauwolfia slows the pulse rate and decreases "reactivity" generally, it lessens the side-effects of hydralazine, such as palpitation and headache. In addition, it appears to potentiate the hypotensive effect of hydralazine, and thereby to lessen the size of dosages necessary to achieve a given lowering of blood pressure. This is very important because the toxic effects of hydralazine (table 2) seem to be at least partly dependent upon the dose. Thus, "sensitivity" reactions to hydralazine in the joints, skin or blood, which at their worst can produce the alarming "lupus erythematosus" syndrome, are uncommon on doses of hydralazine of less than 200 mg. a day. The same may be said of angina pectoris, which hydralazine may cause in patients with coronary disease, apparently because the drug stimulates cardiac output to rise out

TABLE 2

Drugs for Hypertension Hydralazine (Apresoline)

- 1. Moderately hypotensive
- Vasodilator, especially renal
- 3. Stimulates cardiac output 4. Causes tachycardia
- 5. May cause sensitivity (skin, joints, blood)

- 6. May cause angina
 7. May cause "L. E." phenomena
 8. Average daily dose: Apresoline, 200 mg.

of proportion to the ability of the coronary circulation to increase blood supply to the myocardium. Angina is produced infrequently by doses of hydralazine of less than 200 mg. a day but, if it occurs, this is sufficient reason for stopping the drug.

Hydralazine, in spite of producing serious side-effects on occasion, is a very useful antihypertensive drug, particularly in combination with Rauwolfia (or reserpine), with chlorothiazide, or with both. It dilates blood vessels generally (possibly in part through release of histamine), and it acts especially to increase renal blood flow. When started on hydralazine in low dosages (i.e., 10 mg. four times a day), patients may become accommodated

Drugs for Hypertension

Veratrum (Protoveratrine)
1. Moderately hypotensive

Causes nausea and vomiting
 Causes bradycardia
 May cause arrhythmia

 May cause collapse
 Average daily doses: Alkavervir, 10 mg.; protoveratrines A & B, 1 mg.; protoveratrine A, 0.4 mg.

to it without suffering the undue postoccipital headache or palpitation which it usually causes when exhibited at first in the ordinary full dosage (50 mg. four times a day).

Veratrum (table 3) is a potent hypotensive drug, but on long-term administration tends increasingly to cause nausea and vomiting, with the result that it is likely to become less and less useful alone as a hypotensive agent. However, in combination with Rauwolfia (e.g., Rauwiloid plus Veriloid), it is well tolerated, particularly in elderly persons with known or possible coronary disease. I know of no deaths attributable to oral veratrum, a not unimportant consideration in the continued prescription of any drug.

Veratrum is also helpful in slowing the pulse rate in patients who continue to have tachycardia even after several weeks on Rauwolfia. This is particularly important when it is desirable to add hydralazine to the regimen, since veratrum, like Rauwolfia, tends to lessen the tachycardia and palpitation that hydralazine usually causes. If, however, the addition of veratrum to Rauwolfia produces the desired lowering of blood pressure, as, fortunately,

TABLE 4 Drugs for Hypertension Chlorothiazide (Diuril)

Diuretic, saluretic
 Moderately hypotensive (especially as adjunct)

3. Causes hypokalemia
4. May cause hyponatremia
5. May cause alkalosis
6. May cause arrhythmia

6. May cause arrhythmia7. Average daily dose: Diuril, 500 mg.

it may do on occasion, there is obviously no need to add hydralazine to the schedule.

Chlorothiaside (table 4) is a new and interesting addition to the armamentarium against hypertension. A strong diuretic, effective orally, and

essentially free of toxic effects, it is ideal for long-term usage. However, because it is a powerful saluretic agent, precautions are necessary in its continued administration because of its effects in depleting electrolytes, particularly upon the potassium stores of the body.

Chlorothiazide is quite useful in hypertension complicated by congestive heart failure. This is not only because it is a potent mobilizer of edema fluid, but also because it has powerful antihypertensive effects, especially when used in combination with other hypotensive drugs. Congestive heart failure, with either clinically apparent edema, or "preëdematous" retention of salt and water (as revealed by radioisotope dilution technics), is now recognized as a not uncommon cause of resistance to antihypertensive drugs. Thus, patients who previously were found to be very responsive to antihypertensive drugs may become completely resistant, even to the ganglionic blocking agents, when excessive amounts of sodium and extracellular fluid accumulate in their bodies. In this situation, diuresis, as with a parenteral mercurial diuretic, has been found to restore their responsiveness to the antihypertensive action of drugs.

Daily or frequent parenteral mercurial injections are not suitable for long-term usage, for obvious reasons. However, oral chlorothiazide is essentially free of toxicity, is as powerful a diuretic as parenteral mercury, and does not itself become ineffective with continued use. It therefore comes as a great boon for use in patients requiring repeated or continuous diuretic treatment. In addition, chlorothiazide appears to have powerful antihypertensive effects of its own. These characteristics make it particularly helpful for congestive failure or subclinical fluid retention due to hypertensive heart disease.

But even more important, chlorothiazide is highly useful in hypertension when there is no measurable retention of salt and water. Indeed, the drug is capable of exerting its typical antihypertensive effect on continued oral administration at relatively low dosages without affecting measurably the body stores of water or electrolytes. This and other collateral observations have led to the belief that chlorothiazide may have important antihypertensive properties independent of its diuretic effects. Presumably these are due to actions on the kidney, possibly decreasing the production (or increasing the elimination) of circulating pressor materials.

Be that as it may, chlorothiazide is most useful in hypertensive patients who have failed to respond satisfactorily or who have become resistant to other antihypertensive drugs. In this situation, chlorothiazide added to a regimen of other drugs may cause the blood pressure to fall in a dramatic fashion. This may be a particularly gratifying result when previously in such a resistant patient the addition of yet another antihypertensive drug to a regimen of two or three agents had never offered any benefit.

Because chlorothiazide is potent not only as a diuretic but also as an antihypertensive agent, and because in the usual treatment of hypertensive

patients the drug is to be continued for a long time if not indefinitely, certain precautions, particularly as to dosage, are necessary if its possible serious side-effects are to be avoided. First, the dosage of chlorothiazide for hypertensive patients should be kept at the minimum necessary to produce a gradual and reasonable lowering of blood pressure. Thus, the average starting dose to be added in a patient already on an antihypertensive regimen is 125 mg. two to three times a day. This may suffice within a week or two to bring about a sizable lowering of pressure in a gentle, comfortable manner to within safe limits, for example 170/100 mm. of Hg. Initial doses of chlorothiazide as high as 1 gm. two or more times a day seem totally unnecessary unless a massive diuresis is desirable, or unless the patient is in the hospital for treatment of an accelerated or a grave form of hypertension.

Because chlorothiazide can cause hypokalemia, supplements of potassium should be given either in the diet (e.g., orange juice) or as salts of potassium, either in a solution or a tablet. Between 7 and 14 mEq. (0.5 to 1.0 gm. potassium chloride) should be given for each 250 mg. of chlorothiazide. In addition, patients should not take a diet low in sodium if they are to be continued on chlorothiazide, since apparently the kidney will excrete more potassium when sodium is not freely available.

It is remarkable that hyponatremia is so much less common than hypokalemia (10% as compared with 40%) in patients continuing to take chlorothiazide without supplementary potassium. This appears to be due to the activation of sodium-retaining mechanisms (aldosterone) by the diuretic. However, hyponatremia can occur, especially on a low salt diet, as can hypochloremic alkalosis. For these reasons, repeated estimations of serum sodium, potassium, chloride and carbon dioxide should be made during the first few weeks or months of therapy with chlorothiazide.

Because it can have sudden, powerful hypotensive effects, particularly if added to previous potent antihypertensive therapy, such as ganglionic blocking agents or splanchnicectomy, chlorothiazide should be given very cautiously to patients already under treatment, especially if they are elderly or have serious vascular disease, and therefore are liable to have an ischemic accident during a hypotensive episode. Chlorothiazide, presumably by its depletion of the body's stores of salt and water, may bring out postural hypotension markedly in a patient completely free of it after a splanchnicectomy or on ganglionic blocking agents. Therefore, in such individuals it should be instituted in a very small dose (62.5 mg. once to three times a day), while the dosage of any ganglionic blocking agent being used should be reduced roughly by half.

Another precaution concerning the use of chlorothiazide in patients with possible vascular disease involves the matter of ischemic coronary disease. There have been five deaths among a large number of patients with coronary disease given chlorothiazide in this clinic. It is only fair to point out that the drug may not have had anything to do with these deaths, all of which

were "cardiac." Nevertheless, since chlorothiazide may decrease serum potassium and may produce cardiac arrhythmias, either with or without evidence of digitalis toxicity, it is conceivable that the drug may have so altered the sodium-potassium balance in critically ischemic areas of the myocardium that a fatal arrhythmia ensued. For these reasons chlorothiazide is prescribed very cautiously in such individuals, and always with supplementary potassium. Furthermore, chlorothiazide is always deferred in hypertensive patients with coronary disease until other, milder antihypertensive procedures have been tried and proved to be unsatisfactory.

It should be mentioned, however, that certain patients with angina pectoris appear to be remarkably relieved of this symptom by chlorothiazide. These are usually hypertensive patients in whom the drug has had an antihypertensive effect and in whom substernal respiratory distress on exertion appears, at least in retrospect, to have been an important component of their angina. It would therefore seem unwise to condemn the use of chlorothiazide for anginal patients, but rather to recommend that it be used in them only with caution, both as to dosage and as to the prescription of supplementary potassium.

An uncommon, and possibly coincidental, observation in patients taking chlorothiazide is the development of hyperglycemia and glycosuria. I have had two cases, and I have heard of single cases elsewhere. But the question of whether diabetes ever is caused or even is aggravated by chlorothiazide requires further study.

When chlorothiazide is suddenly stopped in a patient to whom it has been given for some days, sodium, chloride and water may be abnormally retained. Presumably this "overshoot reaction" is the result of the continuance of compensating mechanisms (such as aldosterone production) activated by the diuretic effects of this drug. It would therefore seem prudent to taper off the dosage of chlorothiazide, rather than to discontinue the drug suddenly.

Antiserotonins (table 5): Because of the possibility that the antihypertensive effect of Rauwolfia or of reserpine is related to their depleting action on the body stores of serotonin and also because serotonin, as its name implies, is a strong vasoconstrictive agent, synthetic analogues of serotonin have been produced in the hope of finding one that would be an effective antagonist or "antimetabolite" of serotonin. The only one of these that has proved suitable for long-term clinical trial is the Benzyl Analogue of Serotonin (BAS, Woolley). This agent, BAS, turned out to be remarkably similar in its clinical effects to reserpine, which it resembles chemically only in containing an indole nucleus. It also has demonstrable antiserotonin effects in man as well as in laboratory animals. However, since its antiserotonin effects are not very powerful in the dosages that can be tolerated in man without excessive sedation over prolonged periods of time, BAS cannot be said to produce its clinical effects clearly because of its antisero-

tonin action. Work is continuing along this line in the hope of clarifying the nature of action of BAS and other analogues of serotonin in order to establish what role, if any, serotonin may play in arterial hypertension.

In this same connection, iproniazid might be called a "proserotonin" (table 6) because it has been shown to block the enzyme, amine oxidase,

TABLE 5

Drugs for Hypertension Antiserotonin (BAS)

1. Mildly hypotensive

Mildly antiserotonin (clinically)
 Sedative, "tranquilizing"

4. Causes bradycardia

Increases gastrointestinal activity
 Average daily dose: BAS, 100 mg.

which degrades serotonin to 5-hydroxyindoleacetic acid, which is then excreted in the urine. When iproniazid is given to animals, body stores of serotonin are said to rise. It is interesting, therefore, that in hypertensive man the drug used experimentally may have definite hypotensive effects. Indeed, when added to an antihypertensive regimen in some otherwise drugresistant patients, it may lower the blood pressure even though no previous combination of drugs, including chlorothiazide, had proved effective. It frequently causes postural hypotension and other unpleasant side-effects. As in the case of BAS, however, it is not clear whether the hypotensive effect of iproniazid is related to serotonin, or is merely the result of other unrelated pharmacologic actions. Unfortunately, iproniazid may produce serious jaundice, and therefore it should be used with great caution, if at all, in hypertension.

Ganglionic blocking agents (table 7) like surgical splanchnicectomy are apparently slowly being relegated to a position of last resort, if not actual disuse, for the treatment of ordinary essential hypertension. This is not because they are not powerful; rather, it is because they are too powerful,

TABLE 6

Drugs for Hypertension Proserotonin (Iproniazid)

Moderately hypotensive (postural)
 Increases serotonin (animals)

- 3. Stimulates central nervous system ("energizer")
- Decreases gastrointestinal activity
 May cause myalgia, paresthesia
 May cause serious jaundice
- 7. Average daily dose: iproniazid, 75 mg.

or at least too generally powerful. Blocking as they do both sympathetic and parasympathetic impulses indiscriminately at the autonomic ganglia, they usually produce such general and severe side-effects that for continued long-term treatment they are simply too unpleasant to be feasible. Also,

as better nonblocking antihypertensive agents are developed, some of which are suitable for producing dramatic decreases in blood pressure, even in "malignant" or encephalopathic hypertensive crises, there is less and less need to resort to the ganglionic blocking agents. Thus, parenteral injections of reserpine, with or without chlorothiazide or hydralazine, may be as effective in such critical states as are ganglionic blocking agents, without causing the unsteady state and numerous side reactions characteristic of the blocking drugs. Admittedly, reserpine in sizable parenteral doses (2 to 5 mg.) also causes heavy "tranquilization," but this is a matter of little consequence in short-term emergency treatment. As physicians become better acquainted with the use of parenteral reserpine, with or without chlorothiazide, they will undoubtedly use less and less of the ganglionic blocking drugs.

However, I am not prepared as yet to dispense with blocking drugs altogether. Essentially they are nontoxic, their side-effects are due chiefly to their basic activity, and if the dosage is very carefully regulated they can

TABLE 7

Drugs for Hypertension Ganglionic Blocking Agents

- Strongly hypotensive (postural)
 Block adrenergic, cholinergic activity
- 3. Can cause collapse
- Cause serious side reactions
- 5. When stopped, blood pressure overshoots
- 6. Average daily doses: hexamethonium, 500 mg.; pentolinium, 100 mg.; mecamylamine 20 mg.

be relied on to lower the blood pressure safely in almost every case. In addition, a few patients in time accommodate themselves extremely well to these drugs and cease to be seriously disturbed, for example, even by postural hypotension. This is especially true now that chlorothiazide is available as an adjunct to allow smaller doses of the blockers to be effective. Formerly, in a very resistant case, only larger and larger doses of a blocking agent could be resorted to, with, of course, an associated increase in side-effects. If ganglionic blocking agents are stopped suddenly there may be a serious overshoot of the arterial pressure to dangerously high levels, apparently because of the continuance of counteracting mechanisms stimulated during long-term use of the drug. Therefore, as with chlorothiazide, it is recommended that the dosage of blocking drugs be tapered off, not discontinued suddenly in hypertensive patients on long-term therapy.

COMMENT

As one looks back over the development of antihypertensive drugs to this point and attempts to judge the significance and implications of their actions, the following impressions (table 8) are gained:

Table 8 Drugs for Hypertension

Comments

"Nonspecific" except Diuril
 Reducing blood pressure is helpful

Combinations are more active
 Trait to hypertension persists

5. Overshoots occur on stopping treatment
6. Less treatment necessary to hold blood pressure down

7. Role of serotonin questionable 8. Blockers less used today 9. Long persistent trial necessary

Long persistent trial necessary
 Treatment should be given whenever prognosis is poor

1. All the antihypertensive drugs, with the exception of chlorothiazide, appear to be "nonspecific" in that they cause similar hypotensive responses in normotensive and in hypertensive individuals.

2. Reduction of arterial pressure, even by such "nonspecific" agents, appears to be a beneficial if not a life-saving procedure in many hypertensive patients, particularly those with an accelerated phase or a "malignant" crisis.

3. Additive if not synergistic effects can be produced by combining antihypertensive drugs, or by using them in combination with splanchnicectomy.

4. A tendency—if not an innate trait—to hypertension seems to exist in most hypertensive patients, since almost uniformly they become hypertensive again when all therapy is stopped.

5. This trait or tendency apparently is the explanation for the mobilization of counteracting mechanisms to the hypotensive effects of drugs, and explains why the blood pressure overshoots when some of the drugs are suddenly stopped.

6. Although several drugs in combination or in larger doses may be necessary to lower a hypertensive's blood pressure to satisfactory levels, it is often possible after some months to maintain such lower levels on considerably less medication than was required to obtain them initially.

7. Serotonin may play a role in hypertension; but it is not clear whether and how the antihypertensive effects of reserpine, BAS or iproniazid are connected with their effects on serotonin. This matter needs more study.

8. Ganglionic blocking agents are slowly being replaced in the drug treatment of hypertension except as a last resort in very critical or very resistant cases.

9. For the usual ambulatory hypertensive patient a persistent, long-term trial of conservative doses of *Rauwolfia*, veratrum, hydralazine and chlorothiazide *in combination*, if and as necessary, will be reasonably successful.

10. High blood pressure of serious degree is harmful, and it can and should be moderated in almost every case. After rarer causes of hypertension (such as coarctation of the aorta, renal disease, and adrenal tumors with hyperadrenalism or hyperaldosteronism) have been ruled out, antihypertensive drug treatment should be given with determination to lower

blood pressure gradually in every patient in whom the family history and the course of the disease indicate that a shortening of life or a period of invalidism is likely without treatment.

SUMMARIO IN INTERLINGUA

Elevation del pression sanguinee de grado sever es nocive. In quasi omne caso, illo pote e debe esser moderate. Post excluder le causas plus rar de hypertension (per exemplo coarctation del aorta, morbo renal, e tumores adrenal con hyperadrenalinismo o hyperaldosteronismo), un medication antihypertensive debe esser empleate con determination visante al objectivo de reducer le pression sanguinee gradualmente in omne patiente in qui le historia familial e le curso del morbo indica que un reduction del periodo de superviventia o invalidismo es le effecto probabile de non-intervention therapeutic.

Omne le drogas antihypertensive, con le exception de chlorothiazido, pare esser "non-specific," in tanto que illos causa simile responsas hypotensive in subjectos normotensive e in personas con hypertension. Le reduction del pression arterial mesmo per medio de tal agentes "non-specific" pare esser benefic, si non de facto vital, in multe patientes hypertensive, specialmente quando illes se trova in un phase accelerate o in un crise "maligne." Effectos cumulative, si non synergic, pote esser producite per combinar drogas antihypertensive o per usar los in combination con splanchnicectomia. Un tendentia, si non un diathese innate de hypertension pare exister in le majoritate del patientes hypertensive, proque quasi uniformemente illes redeveni hypertensive quando le therapia es interrumpite. Iste facto pare esser le explication del mobilisation de contramechanismos in opposition al effectos hypotensive del drogas; illo explica proque le pression del sanguine resalta a supra su altor original quando certes del drogas es discontinuate subitemente.

Ben que plure drogas in combination o in grande doses es a vices requirite pro reducer le pression sanguinee del patiente con hypertension usque a nivellos satisfacente, il es frequentemente possibile post alicun menses mantener le reducite nivello per medio de considerabilemente minus grande doses de medication que illos initialmente necessari pro effectuar lo. Il es possibile que serotonina ha un rolo in hypertension, sed si e como le effectos antihypertensive de reserpina, del analogo benzylic de serotonina, o de iproniazido es connectite con lor effectos super serotonina non es clar. Iste question require studios additional. Agentes de blocage ganglionic es lentemente reimplaciate in le tractamento medicamentose de hypertension, excepte como un ultime mesura in casos que es multo critic o multo resistente. Pro le usual patiente ambulatori, un persistente e prolongate essayo de doses conservative de Rauwolsia, veratrum, hydralazina, e chlorothiazido—in combination si e quando isto es necessari—promitte un plus o minus satisfacente successo therapeutic.

Tamen, omne iste drogas debe esser usate con certe precautiones, proque illos pote producer adverse effectos lateral, a parte le facto que illos pote resultar in excessos de hypotension. Assi Rauwolfia pote causar depression o etiam hypersecretion gastric; veratrum pote causar nausea, arrhythmia, o collapso; hydralazina pote causar mal de capite, angina, o serie reactiones de sensibilitate; e chlorothiazido pote causar hypokalemia, arrhythmia, o (il pare) mesmo arresto cardiac. Le caute regulation del dosage al nivello del minimo efficace e, in le caso de chlorothiazido, doses supplementari de kalium es importante in le effortio de reducer le effectos lateral de iste drogas.

THE ROLE OF THORACOTOMY IN THE DIFFER-ENTIAL DIAGNOSIS OF PLEURAL **EFFUSION***

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INTRODUCTION

It has long been axiomatic that primary pleural effusion in tuberculinpositive individuals must be considered to be tuberculous until proved otherwise. The basis for this axiom arose in the pre-chemotherapy era when an appallingly high breakdown rate with significant tuberculous manifestations was noted in patients with pleural effusions followed for over five years.

Roper and Waring,1 for instance, reported an over-all five-year breakdown rate of 65.2% in 141 patients treated in Army hospitals in the years 1944 and 1945. The breakdown rate was 90.9% in those patients in their series treated with less than six months of bed-rest, and 30.6% in those patients receiving over six months of bed-rest. Thus, while the tuberculosis relapse rate remained appallingly high, even with the best of treatment, there was certainly a marked difference ascribable to prolonged bed-rest.

Compton 2 is currently reviewing 205 cases treated at Fitzsimons Army Hospital in the years 1953 through 1956, and he has been unable to find any case of relapse to date in any patient who has received adequate chemotherapy by present-day standards. Personal observation by this author would bear out Compton's findings. A great number of patients who were put on temporary retirement from military service following pleural effusion have been observed in follow-up reviews for a considerable period of time. In none of these patients has there been any subsequent breakdown with significant tuberculosis, provided the original course of treatment was adequate.

In view of the high breakdown rate of untreated pleural effusions and the excellent prognosis with adequate treatment, the natural tendency at Fitzsimons Army Hospital, as well as in most other institutions dealing with tuberculosis, is to bend over backward and treat all cases where there is any doubt as to the possibility of a tuberculous etiology of a given pleural effusion. We fully realize that this policy has resulted in unnecessary treatment in many patients who probably were not tuberculous, but in whom the diag-

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nosis of tuberculosis could not be disproved. Because of the danger of withholding treatment, the presumption of guilt until innocence is proved has been the policy in the management of pleural effusion in recent years. Inevitably this has led to a certain amount of unnecessary emotional trauma, family hardship and economic loss. In an economic sense there has been unnecessary cost of hospitalization and treatment, and, in the unique problem which arises in the Armed Forces, we are certain that many have been paid medically unnecessary pensions for many years. Heretofore, this has always been considered a necessary price to pay for the safety of the individual for the reasons outlined above.

From the foregoing, it follows logically that if a method of differential diagnosis could be found which could be relied upon with a high degree of accuracy, it would be possible to eliminate most nontuberculous cases and reserve prolonged chemotherapy for proved or strongly presumptive cases. It would also be possible in many instances to establish a definitive diagnosis for the nontuberculous group of effusions and to institute proper treatment as indicated.

It has seemed to us that, in selected cases, diagnostic thoracotomy with careful examination of the resected material offers a rational approach. However, certain factors must be considered which might possibly limit the value of thoracotomy. Foremost of these is the influence of chemotherapy on the morphology and bacteriology of a pleural effusion. Many cases have been on antituberculous drugs for a considerable period before they are considered for surgery. Most surgeons are loath to operate on cases of possibly active tuberculosis without the adequate preoperative protection offered by chemotherapy. Thus, the influence of these drugs on tuberculous pleuritis will have to be determined.

The next problem is one of surgical exposure. A punch biopsy or limited surgical procedure might pick up a relatively normal area and overlook adjacent significant pathology, and thus give falsely negative results. Breckler, Hensler et al.³ have recently reported on limited open biopsy technic in pleural effusion in a small series of cases. They feel they can differentiate tuberculous effusions from nontuberculous effusions on morphologic bacteriologic grounds in about 80% of cases. This is good but far from ideal, and a number of cases given tuberculosis clearance by use of their technic are liable to subsequent breakdown with significant tuberculosis when their series is large enough. After all, their preliminary estimate would indicate that they will overlook about 20% of cases of tuberculous pleural effusion.

Donohoe et al., in an excellent paper, point out the value of aspiration biopsy of the parietal pleura. In their hands this simple procedure has been without risk, and it establishes a pathologic diagnosis of granulomatous pleuritis in a high percentage of cases without resort to more extensive procedures. However, these authors emphasize that a negative biopsy or find-

ings of nonspecific pleuritis by no means exclude tuberculosis, since a relatively high proportion of their negative needle biopsy findings was found to have granulomatous pleuritis at subsequent open thoracotomy.

Needle biopsy, when positive, would therefore seem to confirm a diagnosis of granulomatous pleurisy, but negative findings are of no value in

their exclusion of tuberculous etiology.

To shed some light on this problem, and possibly to offer better differential criteria for tuberculous versus nontuberculous pleuritis, the records of 63 patients who received open thoracotomy for pleural disease at Fitzsimons Army Hospital during the years 1953 through 1956 have been carefully analyzed and reviewed, and our findings in these 63 cases will form the basis of this paper. A few of these patients were probably included in a previous paper by Stead, Eichenholz and Stauss; ⁵ however, the present review was made independently, and no effort was made to correlate the cases reviewed at this time with the cases reviewed in any previous study.

ANALYSIS OF CASES

Sixty-three cases who received open thoracotomy during the years 1953 through 1956 are reviewed (table 1).

All cases had pleural involvement which either was due to tuberculosis, or at some point in the course of the disease the possibility of tuberculous pleuritis was seriously entertained or could not be clinically excluded.

TABLE 1 Thoracotomy Data on 63 Patients

17 14 32
63
57
6
63
30
1
î
38
25
77
63

The final diagnosis in 38 cases was tuberculosis, and the remaining 25 patients were considered to have nontuberculous pleuritis. The indications for thoracotomy were primarily diagnostic in 17 cases. In 14 cases the indi-

cation was both diagnostic and therapeutic, and in the remaining 32 patients thoracotomy was primarily a therapeutic procedure.

Thus, in half of our cases the operation was done at least in part for diagnostic consideration, and in the other half primarily for therapeutic indications.

In 63 thoracotomies, 57 cases were decorticated and six received open pleural biopsy in the course of a full exploratory thoracotomy.

Pulmonary tissue, either wedge, segment, lobe or limited biopsy, was obtained in 30 of the 63 cases. In one patient a hilar node biopsy was obtained, and in one a cervical node biopsy was obtained at the time of thoracotomy. One patient had a pericardial biopsy.

SKIN TESTS

In the 38 cases with an ultimate diagnosis of tuberculosis the PPD was positive in 35 cases and was not done in the remaining three, each of whom had proved pulmonary tuberculosis with positive sputum. In the 25 cases ultimately given tuberculosis clearance the PPD was positive in 18 and negative in seven. This would indicate that a positive tuberculin proves nothing as to the etiology of a given effusion, but that a negative tuberculin would be strongly presumptive evidence that a given effusion was not tuberculous (table 2).

TABLE 2

Skin Test Results

Tuberculin

Final tuberculosis diagnosis
Final nontuberculosis diagnosis

* All obvious active pulmonary tuberculosis with positive sputum.

Of course, the usual precautions regarding freshly prepared testing solutions, proper reading of skin tests, and repetition of the tuberculin test to rule out tuberculin conversion following acute pleural effusion as a manifestation of acute primary tuberculosis should be observed.

In practically all of our cases, skin tests were also done for histoplasmosis and coccidioidomycosis; eight cases had a positive histoplasmin skin test associated with a positive tuberculin and a negative coccidioidin. Seven cases had a positive coccidioidin associated with a positive tuberculin and a negative histoplasmin. Three patients were positive to all three antigens.

In this series, which represented a high incidence of diagnostic problems, all the positive fungus skin tests occurred in association with a positive tuberculin test. Thus, fungus skin testing added one more diagnostic possibility in 15 cases and two additional possibilities in three cases, but failed to be of any value in eliminating tuberculosis from the differential diagnosis.

In general, therefore, positive skin tests add to the possibilities but diagnose

nothing. However, negative skin tests are of value in eliminating tuberculosis from consideration.

PLEURAL FLUID FINDINGS

In 49 of our 63 patients, one or more taps are recorded. The description of the pleural fluid varies widely from record to record, so that comparison is difficult. However, there do not seem to be any specific characteristics that consistently separate tuberculous from nontuberculous effusions.

Seven of the 49 patients had a culture positive for tubercle bacilli, or positive results from guinea pig inoculation of the thoracentesis fluid on at least one occasion. Positive findings usually were obtained during the initial diagnostic phase prior to any intensive chemotherapy. One patient had a positive smear which was unconfirmed on culture. Positive smears without cultural confirmation are always open to a certain amount of question as to their validity. We are thus left with seven sure and one probable bacteriologic confirmation from tests of the pleural fluid out of 38 proved tuberculous pleural effusions. Pleural fluid bacteriology, therefore, was reliable in proving the diagnosis in only 21% of our tuberculous pleural effusion cases. This percentage is entirely too low to make negative pleural fluid bacteriology of any value in eliminating tuberculosis from the differential diagnosis.

SPUTUM AND GASTRIC ANALYSIS

Sixteen of the 38 tuberculosis patients in our series had at least one positive finding reported on examination of their sputum and/or gastric aspirate. Fourteen of these patients had cultural confirmation, and two had positive smears unconfirmed by culture. It is interesting to note that five of our 16 patients with positive bacteriologic findings had no evidence of parenchymal pulmonary disease clinically, and no evidence of a parenchymal lesion was described at thoracotomy. One patient had no clinical or x-ray evidence of pulmonary disease except for his pleural effusion, but definite evidence of parenchymal tuberculosis was found at surgery. The remaining nine patients had obvious active pulmonary disease.

The foregoing would seem to indicate that a relatively high proportion of patients with pleural effusions have active pulmonary or endobronchial foci so small as to escape detection by conventional methods, but still capable of producing positive bacteriologic findings during the acute phase of the disease if diligently repeated sputums or gastric aspirates are obtained.

On the other hand, positive bacteriologic findings may at times be misleading. One of our patients had two positive sputum cultures reported with negative guinea pig inoculations from these cultures and numerous subsequent negative gastric cultures. His PPD was persistently negative on 12 examinations, and at thoracotomy no demonstrable tuberculosis was found. This man was given final clearance as not having tuberculosis as a result of his thoracotomy findings, which revealed a hiatus hernia and a post-traumatic fibrous pleuritis. It is felt that in this case the positive cultures represented a laboratory error but one which was exceedingly difficult to resolve.

Since only about 40% of our tuberculous effusions had even one single positive bacteriologic finding, and many of these cases had known pulmonary disease in addition to their pleural involvement, it is felt that the incidence of positive sputum or gastric findings is too low to give a reliable index as to whether a given effusion is or is not tuberculous.

PULMONARY AND NONPLEURAL DISEASE

Many of our cases had disease in addition to their pleurisy. For purposes of discussion, the 25 nontuberculous cases will be discussed separately from the 38 cases with a final diagnosis of tuberculosis (table 3).

TABLE 3
Significant Conditions Possibly Related to Pleurisy in 25 Cases with Nontuberrulous Discharge Diagnosis

with Nontuberculous Discharge Diagnosis		
Previous pneumonia Bronchiectasis (surgically proved)	7	
Pulmonary fibrosis and emphysema (surgically confirmed)	2	
Histoplasmosis (surgically proved) Coccidioidomycosis (surgically proved)	1	
Granuloma, etiology undetermined, probably histo- plasmosis or coccidioidomycosis (surgically removed)	1	
Diaphragmatic hernia containing omentum, post-traumatic (surgically diagnosed)	1	
Collagen disease, unclassified, manifested by arthritis and pleural effusion	1	
Rheumatic heart disease with rheumatic pleuritis	1	
Nonspecific pleuritis		
No other condition clinically or found at thoracotomy to explain pleural effusion	7	
Total	25	
1 Outs	40	

Seven of the nontuberculous cases had no demonstrable pulmonary disease preceding or associated with their pleural effusion, either clinically or found at surgery. These seven cases were felt to be nonspecific pleural effusions of nontuberculous origin. The pathologic findings were those of chronic fibrous pleuritis. Seven additional cases had a history of pneumonia preceding their pleurisy. Three patients had surgically proved bronchiectasis associated with pneumonitis and pleural effusion. In two patients, pulmonary fibrosis and/or emphysema was present which may have played some role in the etiology of their effusion. One patient had collagen disease manifested by a rheumatoid type of arthritis and an associated pleural effusion. One patient had an old history of rheumatic fever with rheumatic heart disease, and his pleural effusion was felt to be on a rheumatic basis.

The pathologic findings in this case were compatible with a rheumatic pleuritis.

Three patients had a subpleural pulmonary granuloma discovered and proved at the time of surgery. There was one case of histoplasmosis and one of coccidioidomycosis, and the third case was discharged with the diagnosis of granuloma, etiology undetermined. This man had positive skin tests for histoplasmosis and coccidioidomycosis as well as a positive PPD. The morphology of the resected granuloma was more suggestive of fungus infection than of tuberculosis. One case was discovered at surgery to have a diaphragmatic hernia containing omentum which was associated with a post-traumatic pleural effusion.

Thus we see that 18 of our patients had some underlying involvement which might have explained their pleural effusion, and in nine of these cases thoracotomy either established or confirmed significant pathology which might have been missed clinically or overlooked by limited diagnostic biopsy. To our mind, this would argue strongly in favor of an open exploratory thoracotomy versus a more limited procedure in establishing a satisfactory differential diagnosis.

Table 4
Significant Tuberculous Conditions Associated with Pleural Effusion in

38 Patients with Discharge Diagnosis of Tuberculosis	
Pulmonary tuberculosis Parenchymal disease known prior to thoracotomy Parenchymal disease, unsuspected clinically or by x-ray, discovered	14
and pathologically confirmed as result of thoracotomy Tuberculous pericarditis, clinically unsuspected, diagnosed at thoracotomy	9
Tuberculous meningitis associated with pleural effusion "Pure" tuberculous pleural effusion—no other manifestations of tuberculosis either clinically or at thoracotomy	1 13
Total	38

In our experience the most common causes for nontuberculous pleuritis are, in order of frequency:

1. Nonspecific or idiopathic pleural effusion.

2. Postpneumonic pleural effusion.

3. Pleural involvement secondary to bronchiectasis or granuloma.

Of the 38 cases given a discharge diagnosis of tuberculosis (table 4), pulmonary tuberculosis was known and established prior to surgery in 14 cases. In 13 cases no pulmonary disease was clinically demonstrated and no pulmonary parenchymal involvement was found at surgery. In nine patients there was no clinical or x-ray evidence of any disease other than pleural effusion; however, definite pulmonary lesions were palpable and removed at thoracotomy. In one patient an unsuspected tuberculous pericarditis was discovered at surgery. One patient had a pleural effusion following a proved tuberculous meningitis with no evidence of pulmonary

disease and nonspecific pleural findings at thoracotomy. This case will be discussed in detail later on in the paper.

We feel it is highly significant that, in 10 out of 38 cases, important evidence of tuberculosis other than pleurisy, unsuspected clinically or by x-ray, was discovered at thoracotomy. This would help to explain the not uncommon clinical observation that a positive sputum or a positive gastric aspirate may be found in what appears clinically to be a pleural effusion, without other demonstrable disease. We feel that this is an important argument in favor of full exploratory thoracotomy as opposed to the more limited biopsy procedures.

The high coincidence of small but definite parenchymal foci in cases of tuberculous pleural effusion has been noted by many observers for a great many years, and is by no means an original observation. Stead et al.⁶ report that in 12 out of 15 patients with tuberculous pleural effusion, definite subpleural parenchymal foci were demonstrated at the time of thoracotomy.

PATHOLOGIC FINDINGS

The original pathology reports were reviewed and the cases were classified as tuberculous or nontuberculous on the basis of these reports, as follows:

Nonspecific inflammatory change or definitely nontuberculous pathology was reported in 28 cases. Tuberculous pleuritis or granulomatous pleuritis compatible with tuberculosis was reported in 32 cases. In three additional cases the pleural biopsy findings were nonspecific, but definite tuberculosis was confirmed by pulmonary tissue removed at the time of surgery (figure 1). Thus, in 32 of 38 cases the pleural pathology was confirmatory and the combined pleural and pulmonary tissue pathology confirmed the diagnosis in 35 of 38 cases in this series, and for an accuracy of approximately 92%. In three cases there was considerable disagreement, negative pathologic findings having been obtained, but a final diagnosis of tuberculosis was nonetheless made. These three cases will be reported in considerable detail. However, it would seem to us that open thoracotomy with adequate exploration should confirm or exclude the diagnosis of tuberculosis in almost all cases, and it should permit us to make a valid presumptive diagnosis of no tuberculosis if the pathology findings at full thoracotomy failed to reveal any evidence of granulomatous pleuritis and no granulomas were palpable in the lung.

In order further to confirm or deny the validity of the pathologic findings, the slides of all 63 cases were submitted without any clinical information for review by the pathologist co-author (H. H. H.) and were classified on the basis of morphology as definite tuberculosis, probable tuberculosis, borderline granuloma, or definite nontuberculosis, according to the following criteria:

Definite tuberculosis (organized caseating granuloma, figure 2): A granuloma consisting of a circular or oval arrangement of tangled or pali-



Fig. 1. Biopsy specimen, showing normal pleural with subpleural pulmonary tuberculous granuloma.

saded epithelioid cells, containing Langhans' type giant cells, surrounding a central mass of eosinophilic granular of fibrillar necrotic material. The nodule is circumscribed by a narrow rim of loose fibroblastic or fibrous con-



Fig. 2. Definite tuberculous pleuritis-organized caseating granuloma.

nective tissue, infiltrated and surrounded by lymphocytes. The presence of acid-fast bacilli on appropriate staining is also considered as confirming definite tuberculosis.

Probable tuberculosis (organized noncaseating granuloma, figure 3): A



Fig. 3. Probable tuberculous pleuritis-organized noncaseating granuloma.

granuloma having the same appearance as described above, but without central necrosis.

Borderline granuloma (morphologic commitment impossible, figure 4): Irregular, often fusiform collections of lymphocytes situated in fibrous tissue



Fig. 4. Borderline granulomatous pleuritis—fibrous tissue, lymphocytes, giant cells and a few epithelial cells. Lesion is neither discrete nor circumscribed.

and associated with giant cells of the foreign-body type. There may be foamy macrophages, granulation tissue and even necrosis. Epithelioid cells are rare. The lesion is neither discrete nor circumscribed by loose fibrous tissue.



Fig. 5. Definitely nontuberculous pleuritis—nonspecific inflammatory reaction with no morphologic features suggestive of tuberculosis.

Definite nontuberculosis (figure 5): Mature fibrous connective tissue marked by diffuse and focal collections of lymphocytes, plasma cells, eosinophils or even neutrophils.

Comment: These criteria are based on the assumption that the disease

process is still relatively recently active. Completely healed tuberculous pleuritis may not differ from non-tuberculous pleuritis in its histologic appearance.

Table 5
Pathologic Diagnosis Based on Study of Resected Specimens

		culous ritis	Nondiagnostic Pleural Find- ings, TB Diag-	Total Path. Diagnosis	Borderline	Definite	Slides Lost or not	
	Definite	Probable	nosed on Basis of Resected Pulmonary Tissue	of TB or Prob- able TB	Granu- loma	Non-TB Diagnoses	Definitely Identified	Total
Original pathology report	33	2*	. 3	35	0	28	0	63
Review of slides sub- mitted as unknowns	27	1	5	33	3	26	1	63

^{*} No division as to definite or probable.

Table 5 demonstrates that this review, within small limits of error, concurs with the results obtained on review of the original pathology reports. It is thus felt that morphologic criteria should be quite satisfactory in separating tuberculous from nontuberculous lesions.

CASE REPORTS

Cases in Which the Morphologic Diagnosis Differed from the Final Diagnosis

Case 1. A 25 year old Negro private was admitted to Fitzsimons Army Hospital in December, 1952, following a spontaneous pneumothorax on the right, at which time x-ray revealed moderately advanced right upper lobe tuberculosis. PPD No. 1 was positive. Sputum was positive for tuberculosis organisms on concentrate and culture from December, 1952, through February, 1953. Subsequent cultures were all negative. Following his spontaneous pneumothorax the patient developed a tuberculous empyema on the right, with pleural fluid which at first was clear and later was purulent. A positive culture for tubercle bacilli was obtained from the pleural fluid on February 24, 1953.

On July 16, 1953, following six months of therapy with streptomycin and isoniazid (INH), the patient had a decortication on the right for treatment of empyema. No pulmonary tissue was obtained at the time of surgery. The pleura revealed non-specific inflammatory pleuritis. Tissue sections, smears and cultures of the decorticated pleura were all negative for tubercle bacilli.

On April 1, 1954, at which time the patient had received 15 months of streptomycin-INH therapy, he had an excision of his sinus tract and drainage of a mixed infection empyema. Again the pathology showed nonspecific pleuritis, and the bacteriology was all negative.

The patient was discharged on September 30, 1954, with inactive tuberculosis, and at the time of his latest follow-up (August 6, 1956), he was clinically well and working.

Review of tissue sections submitted as "unknown" at the time of the present study also resulted in a diagnosis of nonspecific inflammatory pleuritis and the sections were classified as definitely "nontuberculosis."

Comment: This patient appears to represent a "clean miss" as far as the pathology is concerned. He had a well documented case of tuberculosis with a positive culture of the pleural fluid five months prior to his original surgery. It is conceivable that mixed infection elements were present in this empyema which completely obliterated the expected morphologic findings of tuberculous granulation tissue. Indeed, this is the only possible explanation in this case. Since no indication existed clinically for resectional surgery in this patient, no lung tissue was removed. However, had this been done, there is no doubt that pathologic confirmation of his pulmonary tuberculosis would have been obtained.

Case 2. A 19 year old Negro female in August, 1954, developed meningeal symptoms accompanied by a left-sided pleural effusion. PPD No. 1 was positive. Spinal fluid revealed 250 white blood cells with 98% lymphocytes; sugar, 38 mg. %; protein, 360 mg. Cultures of the spinal fluid, as well as repeated sputums and gastric aspirates, were all negative for tubercle bacilli. No thoracentesis was ever performed.

The patient was placed on intensive antituberculous therapy, with immediate, dramatic clinical improvement, and was clinically perfectly well at the time of surgery.

On June 1, 1955, the patient received a left decortication for residual pleural thickening with functional impairment of the left lung. At the time of surgery she had received six months of triple drug therapy, plus four additional months of streptomycin-INH.

The pathologic findings were those of chronic fibrous pleuritis. Tissue sections,

smears and cultures were all negative for tubercle bacilli.

The patient was discharged on August 6, 1955, as inactive tuberculous meningitis and inactive tuberculous pleural effusion. Her last follow-up was on March 26, 1957, at which time she remained perfectly well.

Review of pleural sections at the time of the present study again resulted in the

diagnosis of chronic fibrous pleuritis, definitely nontuberculous.

Comment: In this case the presumption of tuberculous meningitis with tuberculous pleural effusion is exceedingly strong clinically, even though it was never proved bacteriologically. Since the effusion was part of an acute manifestation of early disseminated disease and the patient had received adequate intensive chemotherapy prior to surgery, it is felt that this patient very likely had had a complete cure of her tuberculous pleuritis by the time of surgery.

Case 3. A 30 year old white male sergeant had had a pneumonic process in the right hilar area in June, 1953, following which he had had six or seven repeated attacks of right-sideu pleuritic pain prior to his admission in June, 1955, at which time he had considerable pleural thickening on the right side, and repeated attempts at thoracentesis were all unsuccessful.

This patient had a positive PPD skin test, in addition to which he had positive histoplasmin and a positive coccidioidin skin tests. Serologic studies for fungi were all negative. His sputum was reported as positive for tubercle bacilli on direct

smear on June 7 and June 8, 1953, prior to this admission to Fitzsimons Army Hospital. Both of these positive smears were subsequently reported as negative on culture. A great number of subsequent sputum and gastric cultures were all reported as negative.

On November 14, 1955, following five months of streptomycin-INH therapy, a diagnostic right thoracotomy with a decortication was done. The pathologic findings were those of chronic fibrous pleuritis. No evidence of granuloma was found, and all bacteriologic studies were negative. Despite the pathology report the patient was still considered to have tuberculous pleural effusion and was continued on chemotherapy to the time of discharge, with a diagnosis of inactive pleural effusion, on November 26, 1956.

Review of pathologic slides as "unknown" during current study also resulted in a diagnosis of chronic fibrous pleuritis, definitely not tuberculous.

Comment: This case has been classified as tuberculous because of the final clinical diagnosis. However, on careful review of this case we believe there is considerable doubt as to the validity of the diagnosis of tuberculosis.

Two positive sputum smears with negative cultures of the same material would seem to cast doubt on the validity of the positive smear. This is especially true in view of the great number of negative cultures before and since. It seems quite likely that this was a case of nonspecific pleuritis arising on a postpneumonic basis, and probably never was tuberculosis. We would suspect that in this case the pathologic diagnosis was right and the clinical diagnosis was roneous.

On review of the see cases of clear disagreement, we would conclude that in case 3 the clinical diagnosis rather than the pathologic diagnosis would seem to be in error. In case 2, where the effusion was associated with an acute tuberculous meningitis, it is entirely conceivable that the patient may have had a true cure prior to the time of her surgery. This would leave only case 1, where there was a chronic tuberculous empyema in which we feel the pathology failed to show the expected findings. It is therefore quite likely that the morphologic findings in this series were even more accurate than the 92% claimed for them.

BACTERIOLOGIC FINDINGS ON RESECTED SPECIMENS

Thirty-five of our 38 cases with a final diagnosis of tuberculosis were shown to have had morphologic confirmation on the basis of material obtained at thoracotomy. Twenty-five of these cases had some form of bacteriologic confirmation, for an incidence of 65.8%. Only one patient had positive tissue sections, smears and cultures of the resected specimen. Twelve patients had positive tissue sections and smears but negative cultures. Seven patients had positive smears only, with negative tissue sections and cultures, and five patients had positive tissue sections with negative smears and cultures. Ten patients (26.4% of our tuberculosis cases) had morphologic findings compatible with tuberculosis but no bacteriologic confirmation of any kind, and three patients (7.8% of the tuber-

culosis patients) were diagnosed tuberculosis though pathologic or bacteriologic proof was not obtained from the resected specimens. These three cases were described in detail in the preceding section.

THE INFLUENCE OF CHEMOTHERAPY ON THE BACTERIOLOGIC FINDINGS AT SURGERY

Fifty-four of our 63 patients received some form of antituberculous chemotherapy prior to surgery, in courses ranging from two weeks to 26 months. The over-all average duration of chemotherapy prior to surgery in these 54 patients was six and one-half months. Thirty-seven patients received streptomycin-INH. Nine patients received streptomycin-INH-para-aminosalicylic acid (PAS) either as triple therapy or in varying combinations. Five patients received streptomycin and PAS. Two received streptomycin-INH and Terramycin in varying combinations, and one received streptomycin-INH-PAS and Terramycin in varying combinations.

In general, the longer the duration of chemotherapy prior to surgery the less chance there is for bacteriologic confirmation. In individual cases, however, there may be wide variance. In our series, patients were noted to be negative bacteriologically although positive morphologically after as little as two months of preoperative chemotherapy. On the other hand, smears or tissue sections were noted to be positive after as much as 26 months of preoperative therapy.

However, the average duration of chemotherapy in cases having morphologic evidence of tuberculosis without any bacteriologic confirmation was three months longer prior to surgery than in those cases in whom positive

smears or tissue sections were obtained.

Chemotherapy of any duration virtually eliminates positive cultures obtained from the resected specimen. The only case in our series with cultural confirmation postoperatively was the single untreated tuberculosis case. The specific drug regimen used does not seem to be important in determining whether bacteriologic confirmation will be found on the resected specimen. The important factor is the duration of chemotherapy prior to surgery. It may also be concluded that chemotherapy per se, regardless of duration or drug regimen used, does not seem to alter the morphologic features significantly, so that a presumptive diagnosis on the basis of histopathology is possible in nearly all cases despite chemotherapy.

Table 6 summarizes the foregoing conclusions regarding the influence of chemotherapy on the histopathologic and bacteriologic findings in 38 pa-

tients with a discharge diagnosis of tuberculous pleuritis.

FOLLOW-UP DATA

The only way we can confirm that the patients given a nontuberculous diagnosis were indeed nontuberculous is by adequate follow-up. All 63 of

Influence of Chemotherapy on Histopathologic and Bacteriologic Findings in 38 Patients with Discharge Diagnosis of Tuberculous Pleuritis (With or Without Associated Pulmonary Tuberculosis) TABLE 6

	Number	Histopath.	AFB Tissue	AFB Cult.	Chemoth	Chemotherapy Preoperative (Months)	operative		Regi	Regimen (Number of Patients)	iber of Pat	ients)	
Group	of Fa- tients in Group	(Pleura and/or Lung)	Sec. or Smear of Specimen	Resect. Specimen	Min.	Мах.	Aver.	None	SM	SM PAS INH	SM	SM INH TM	SM-PAS- INH-TM
I Unconfirmed	3	Negative	Negative	Negative	10	15	10.0	0	2	1	0	0	0
II. Morphologic confirmation only	10	Positive	Negative	Negative	2	26	9.2	0	4	8	-	-	-
Morphologic AFB smear or section	24	Positive	Positive	Negative	1.5	23	6.2	0	81	3	2	0	0
IV Morphologic culture	1	Positive	Positive	Positive	0	0	0	1	0	0	0 .	0	0
Totals:	38 100%	35 Pos. 3 Neg. 92.7% Pos.	25 Pos. 13 Neg. 65.8% Pos.	1 Pos. 37 Neg. 2.67% Pos.	1.5	26	6.2	2.6%	24 63.2%	63.2% 18.4%	3,67	5.3%	2.6%

our patients had had maximal benefit of hospitalization at the time of their discharge. All tuberculous cases were classified as either inactive or arrested at the time of discharge. In 45 cases information was available six months or longer from the date of discharge. Eighteen patients were lost to follow-up, or no information was available six months or longer after discharge.

Table 7 shows the duration of follow-up in years of the 71% of our patients on whom follow-up information is available.

TABLE 7

Vears from Fitzsimons Army
Hospital Discharge

3-3\frac{1}{2}
2\frac{1}{2}
3
2-2\frac{1}{2}
1\frac{1}{2}
1-1\frac{1}{2}
1
Total

Total

Number of Patients

4
8
5
11
13
4
45 (71%)

All 45 of our patients with follow-up data available are essentially well. Most are gainfully employed. None is disabled for medical reasons related to his illness. None of the tuberculous patients has relapsed, and none of the patients given tuberculosis clearance has developed evidence of tuberculosis since the time of discharge.

LIMITATIONS AND PLANS FOR FURTHER STUDY

The primary purpose of this study has been to ascertain the reliability of morphologic findings from tissue obtained at thoracotomy in differentiating tuberculous from nontuberculous effusions.

While it appears to us that this seems to be a reliable method in the vast majority of cases, we are well aware that certain criticisms can be leveled at a retrospective study of this type.

First, our series of 63 cases with relatively short-term follow-up might be considered to be too small and too premature to be of much statistical significance.

Second, only eight of the 25 nontuberculous patients received no chemotherapy prior to or following surgery. In the remaining 17 nontuberculous cases the average duration of chemotherapy approximated six months. It is possible that erroneous tuberculosis clearance might have been given in some of these cases, but that the intensity and duration of chemotherapy were great enough to produce healing and prevent relapse. We are therefore inclined to view this study as a preliminary report which would indicate the validity of our thesis rather than establish its incontrovertible truth.

Bearing these facts in mind, we have set up a protocol for a controlled study in cases of pleural effusion of dubious etiology, eliminating those cases that, on clinical and bacteriologic grounds, are definitely either tuberculous or nontuberculous.

The patients in this study are to be given a short period of preoperative drug coverage, followed by limited thoracotomy with pleural biopsy, such as is advocated by Breckler et al.³ The tissue obtained is to be separately labeled for examination. The incision is then to be extended and a full exploratory thoracotomy, with careful palpation of the lung and removal of specimens for examination, is to be carried out. All cases shown to be tuberculous or probably tuberculous on morphologic and/or bacteriologic grounds will receive full courses of antituberculous therapy.

In all cases in whom the bacteriology is negative and the morphology is nontuberculous by the criteria set forth earlier in this paper, all antituberculous drugs are to be immediately discontinued and the patient is to be returned to a full activity status immediately following recovery from surgery. This will include returning military patients to a full-duty status.

All patients will be placed on a regular follow-up schedule and observed at frequent intervals for a period of five years following their surgery. In this manner, if we are wrong no great harm will have been done, since any tuberculous relapses in the supposedly nontuberculous group will come under prompt and adequate medical care. If we are correct in our assumption, there should be a negligible relapse rate in the nontuberculous group.

This study will also give us an opportunity to compare the relative diagnostic accuracy of full exploratory thoracotomy versus limited pleural biopsy procedures in a large number of cases, using each patient as his own control, since both procedures will be carried out by the same surgeon at the same time and examined by the same pathologist using identical technics and diagnostic criteria on both specimens. We would anticipate that full thoracotomy will be confirmed as showing greater reliability than does limited open pleural biopsy.

Should the long-term study bear out the findings indicated in this preliminary report, we feel that we will have added a valuable tool to our diagnostic armamentarium which, when wisely used under proper circumstances, could result in considerable saving in time, family hardship and expense in many instances.

While we are embarking on the study outlined above, it should be emphasized that we are not advocating indiscriminate use of exploratory thoracotomy in all cases of pleural effusion, but are reserving this recommendation for those cases in whom there is some legitimate doubt as to the diagnosis and in whom it is felt necessary to avoid prolonged hospitalization or chemotherapy if it can be reasonably demonstrated that the patient probably does not have tuberculosis.

SUMMARY

1. In an effort to establish better criteria for the differential diagnosis of pleural effusion, the records of 63 cases with pleural disease who received

open thoracotomy have been reviewed. In all of these cases a diagnosis of tuberculosis either was established or was a strong differential diagnostic possibility. All patients received an open thoracotomy for either diagnostic or therapeutic indications, or both. Thirty-eight patients were given a final diagnosis of nontuber-

culous pleuritis.

2. The tuberculin tests show positive in all patients with the final diagnosis of tuberculosis. All negative tuberculins were in the nontuberculosis group. It is felt that a negative tuberculin test, done with properly prepared solutions and repeated six to eight weeks after the onset of the effusion, effectively excludes tuberculosis as the cause of a given pleural effusion. However, positive tuberculin tests prove nothing as far as establishment of a tuberculosis diagnosis is concerned other than the fact that tuberculosis must be considered as a possibility.

3. Other skin tests, such as histoplasmin or coccidioidin, may add to the differential diagnostic possibilities but prove or disprove nothing in the

individual case.

4. The pleural fluid showed no consistent physical, chemical or morphologic differences that could be relied upon to differentiate tuberculous from nontuberculous effusions. Only 21% of the patients with a final diagnosis of tuberculosis had positive bacteriologic findings on the pleural fluid aspirate. Bacteriologic diagnosis on pleural fluid is therefore helpful only in a positive way, but negative findings do not exclude tuberculosis.

5. Positive sputum and/or gastric aspirates were found at least once in about 40% of our tuberculous patients. Frequently, one or more positives were found in patients having pleural effusions with no x-ray evidence of parenchymal disease. Nonetheless, the incidence of positive sputum or gastric findings is too low to be cf differential diagnostic value in the negative sense. However, positive bacteriologic findings, even in what appears to be "pure" pleural effusion, are probably an indication of underlying active parenchymal or endobronchial disease.

6. Full open exploratory thoracotomy in doubtful cases seems to be more valuable than does limited thoracotomy or closed biopsy technics. Not only can better areas be selected under direct vision for biopsy, but also significant pulmonary lesions are frequently found which otherwise might be undetected.

Nine of the 25 nontuberculous cases had significant pathologic findings other than pleural, either established or confirmed on the basis of thoracotomy which might otherwise have been overlooked. In 10 of the 38 tuberculous cases significant nonpleural tuberculosis was found which was unsuspected either clinically or by x-ray.

7. Morphologic pleural changes established the presumptive diagnosis of tuberculosis in 32 of 38 cases. In three additional cases the diagnosis was established by the morphology of lesions discovered in the lung at the time of surgery. Thus, morphologic changes in the pleura and/or the lung

established a diagnosis in 35 of 38 cases. The additional three cases would never have been diagnosed had not full open thoracotomy with careful palpation of the lung been done. More limited procedures might well have overlooked these cases.

8. The three cases of disagreement between morphologic findings and final diagnoses are analyzed in detail, and it appears that in only one of these three is there no reasonable explanation for the disparity.

9. Morphologic findings on the basis of tissue obtained at open thoracotomy are therefore at least 92% reliable in the present series in differentiating tuberculous from nontuberculous pleural effusions.

10. Morphologic findings are unaffected even by prolonged preoperative chemotherapy in practically all cases.

11. Bacteriologic confirmation of morphologic findings by acid-fast stains of tissue section, smears, or cultures on resected specimens was found possible in 65.8% of the tuberculous patients. In only one patient, however, was it possible to get cultural confirmation.

12. The chance of bacteriologic confirmation of the resected specimen is inversely proportional to the duration of preoperative chemotherapy. The specific drug regimens used do not seem to be important.

13. Follow-up information of from six months to three and one-half years after discharge is available in 71% of our cases. There has been no tuberculosis relapse, and no patient cleared as nontuberculous pleurisy has broken down with clinical tuberculosis to date.

14. The limitations of this retrospective study are discussed, and plans for future study and follow-up of a series of patients are outlined.

Conclusions

1. In cases of idiopathic pleural effusion it would appear that the best way to make an etiologic differential diagnosis of tuberculous versus non-tuberculous origin is by means of an open exploratory thoracotomy, with removal of an adequate area for biopsy from the involved pleura. A specimen of lung should be obtained when pulmonary involvement is found.

2. Morphologic and bacteriologic studies should be done on the resected specimen and should be of differential diagnostic value in almost all cases.

3. Morphologic change is unaffected by preoperative chemotherapy, but the chances of bacteriologic confirmation are inversely proportional to the duration of preoperative chemotherapy.

4. Results of this retrospective study on 63 cases would indicate at least 92% reliability of full exploratory thoracotomy in establishing a differential diagnosis of tuberculous versus nontuberculous pleural effusions on morphologic criteria.

5. There seems to be a strong indication for a controlled study utilizing exploratory thoracotomy in effusions of dubious etiology. Except for a short period of preoperative drug coverage in all cases, antituberculous

chemotherapy should be withheld in all patients who do not exhibit morphologic or bacteriologic changes compatible with tuberculosis. A long-term follow-up study on such a series of cases would seem to be of great value.

6. A five-year follow-up study, as in scated above, is currently being established at Fitzsimons Army Hospital, and it is to be hoped that other institutions will do likewise.

SUMMARIO IN INTERLINGUA

Iste studio es basate super le detaliate analyse de 63 patientes subjicite a thoracotomia aperte pro morbo pleural al Hospital Militar Fitzsimons durante le annos 1953 a 1956. In 38 patientes le diagnose final esseva tuberculose; in 25 patientes le

diagnose final esseva nontuberculotic.

Le objectivo del presente articulo es evalutar le varie manovras de diagnose differential que es usate in effusion pleural, discuter le valor relative de iste manovras, e establir le valor del morphologia como un bon criterio del diagnose differential. Le effecto del chimotherapia super le morphologia e etiam super le bacteriologia es discutite. Super le base de iste studio, il es postulate que le complete thoracotomia aperte es superior al biopsia a agulia o al technica del limitate biopsia aperte.

Significative conditiones tuberculotic e nontuberculotic es discoperite como resultato de thoracotomia aperte in casos ubi plus restringite manovras haberea lassate los escappar al detection. Es opinate que thoracotomia aperte ha un accuratia de circa 95% in le differentiation inter effusiones tuberculotic e nontuberculotic.

Super le base del reportos pathologic original e etiam super le base del resultatos de un examine del specimens (non identificate) per un membro del departimento de pathologia (Capitano Harrison), il esseva establite que le morphologia es valide como criterio differential in separar le typo granulomatose ab le typo non granulomatose de pleuritis, sin reguardo al duration del previe curso de chimotherapia.

Le effectos de chimotherapia preoperatori es enalysate. Il pare que le prospecto de obtener un confirmation bacteriologic super le base del specimen de resection decresce in proportion al augmento del duration del chimotherapia preoperatori. Tamen, confirmation pathologic super le base del morphologia pote esser obtenite in quasi omne le casos in despecto del chimotherapia preoperatori.

Stimulate per le resultatos del presente studio nos ha initiate un studio de protocollo utilisante thoracotomia in le diagnose differential de effusiones pleural.

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EFFECTS OF SUBLINGUAL NITROGLYCERIN ON PULMONARY ARTERIAL PRESSURE IN PATIENTS WITH LEFT VEN-TRICULAR FAILURE * †

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THE retrosternal distress associated with paroxysmal dyspnea may be quite severe, and in many instances it is described by the patient as pain.1 This discomfort is sometimes interpreted by the physician as the pain of angina pectoris, resulting in the administration of nitroglycerin.

In a recent publication we reported that frequently the retrosternal discomfort and breathlessness of paroxysmal dyspnea were promptly relieved by the sublingual administration of nitroglycerin. The clinical effectiveness of nitroglycerin over other emergency measures was so unmistakable in many of our patients that we now use the drug routinely, and the patients now insist on having the drug available for use during episodes of paroxysmal dyspnea. Further, we reported that in patients with hypertensive left ventricular failure, studied by right heart catheterization, nitroglycerin administration resulted in a prompt reduction in the associated pulmonary hypertension.2

We wish to report further observations on the hemodynamic alterations produced by nitroglycerin administration in hypertensive left ventricular failure, including changes in pulmonary vascular resistance. Hemodynamic observations are also presented in one patient who spontaneously developed angina pectoris during the control period after the catheter had been positioned in the pulmonary artery and who made an uneventful recovery following nitroglycerin administration.

MATERIALS AND METHODS

The clinical diagnosis in the patients studied was left heart failure, or both right and left heart failure. One patient had coronary arteriosclerotic heart disease with angina pectoris. Most of the patients were known to

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have hypertensive heart disease. The general characteristics of the patients used in this study are listed in table 1.

Hemodynamic data were obtained using standard right heart catheterization procedures. The cardiac outputs were determined by the direct Fick method. Oxygen consumption was calculated from expired air samples collected in a Tissot spirometer and analyzed with a Scholander gas analyzer. Direct measurement of the brachial artery pressure was made through an indwelling needle simultaneously with the measurement of pressure in the pulmonary artery.

TABLE 1
General Characteristics of Patients*

				Blood I	ressure	Circula
Case No.	Sex	Age	Clinical Diagnosis	Systemic mm. Hg	Venous mm. H ₂ O	Timet sec.
1	M	39	Heart failure (etiology undetermined)	164/104	300	67
2 3	M	42	Heart failure (etiology undetermined)	99/78	330	35
3	M	35	Heart failure (etiology undetermined)	116/82	135	16
4	F	51	Hypertensive and arteriosclerotic heart disease	181/107	202	19
5	M	43	Hypertensive heart disease	160/102	105	16
6	M 40 Hypertensive heart disease		164/106	94	17	
7	F	74	Hypertensive heart disease	195/129	240	20
5 6 7 8 9	M	50	Hypertensive heart disease	199/132	284	35
9	M	52	Hypertensive heart disease	195/129	336	45
10	F	54	Hypertensive heart disease	280/134		26
11	M	65	Hypertensive heart disease	260/140	176	72
12	F	64	Hypertensive and arteriosclerotic heart disease	160/80	230	25
13	M	54	Arteriosclerotic heart disease, angina pectoris	150/90	110	15

* In all cases heart enlarged on x-ray study and electrocardiogram abnormal, showing ST-segment and T-wave changes interpreted as evidence of myocardial damage.

† Arm-to-tongue method.

After control cardiac outputs and pressure measurements were made, nitroglycerin (0.6 mg.) was administered sublingually. Following nitroglycerin administration, cardiac outputs and pressure measurements were repeated at short intervals during the succeeding 30 minutes. The pulmonary "wedge" pressure was obtained by the method of Hellems and associates.⁸

RESULTS

The mean pressure in the pulmonary artery was elevated during the control period in all the cases. In nine of the cases a reduction in pulmonary artery pressure was noted within five to 15 minutes after nitroglycerin administration. By the end of 30 minutes, however, a reduction in pulmonary artery pressure was observed in all 13 cases (table 2). There was a tend-

ency for the pulmonary artery pressure to return toward the control level by the end of 45 minutes, but in one case where pressure measurements were continued the maximal fall persisted beyond 45 minutes.

In another patient a repeat dose of nitroglycerin, administered 45 minutes after the first, promptly resulted in a second drop in pulmonary artery pressure (figure 1).

Although the pulmonary artery pressure fell in all patients during the first 30 minutes following nitroglycerin therapy, in three of the patients (cases 9, 11 and 12) the fall did not exceed 10% of the control and was considered to be insignificant. These three patients were all in severe intractable hypertensive heart failure. In addition, these patients showed no significant fall in their systemic mean pressure following nitroglycerin therapy.

TABLE 2
Changes in Mean Blood Pressure 5 to 15 and 16 to 30 Minutes
Following Nitroglycerin Administration

	Puh	monary Art	tery	Br	achial Arte	ry	"Pulr	monary Wedge"		
Case			t Change		Per Cent	Change	0	rer Cen	t Change	
	Control	5-15	16-30	Control	5-15	16-30	Control	5-15	16-30	
1	20	-30	-20	122	-11 -30		-			
2	35	+6	-29	103	+3	-1		11.7		
3	30	-27	-23	90	-6	+2				
4	48	-6		135	-24	-	33			
5 6 7 8	26	-27	-31	118	-3	-16	18	-17		
6	36	-3	-36	115	-20	-32	23		-17	
7	36	-53	-55	124	-19	-39	19			
8	65	-11	-11	131	-3	-2	36	-36		
	58	-10	-3	151	-2	-1				
10	38	-58	-58	180	-17	-14				
11	43	-2	-2	168	-5	+1	28	-64		
12	60	-3	-5	93	+3	+10				
13*	72	-68	-72	148	-20	-27				
verage		-22	-28		-9.5	-10				

^{*} During angina pectoris attack.

In case 9 the pulmonary artery pressure showed no significant drop after nitroglycerin, but neither was there a decrease during a 60-minute period after 1.25 mg. Digoxin had been given intravenously.

An attempt was made to measure the pulmonary "wedge" pressure in all of these patients. In six of the cases, control wedge pressure measurements were successful, all of which were elevated. In four of the six, post-nitroglycerin wedge pressure measurements were obtained and demonstrated a significant reduction which appeared to persist (figure 2).

The behavior of the total pulmonary artery resistance and the pulmonary arteriolar resistance following nitroglycerin administration in patients with

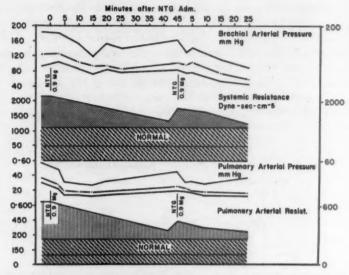


Fig. 1. Hemodynamic effects of repeated doses of nitroglycerin in left ventricular failure (case 7).

left heart failure is of considerable interest in that this behavior might provide some clarification of the mechanism of action of nitroglycerin. As noted above, we were successful in obtaining postnitroglycerin wedge pressures in only four of the cases. The lack of these data prevented the calculation of the arteriolar resistance for the group of cases.

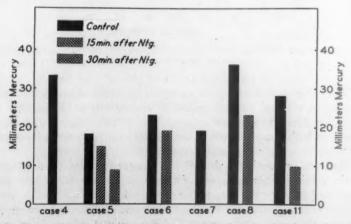


Fig. 2. Changes in pulmonary "wedge" pressure following nitroglycerin administration.

An estimate of the behavior of the total pulmonary resistance for the group was possible using the formula $\frac{P_A \text{ mean} \times 1.332 \times 60}{\text{Cardiac output L/min.}}$. As can be seen in figure 3, there was a prompt fall in the total pulmonary resistance in 12 of the 13 cases within the five- to 15-minute period after nitroglycerin administration. This finding, along with the fall in the pulmonary wedge pressure in the four cases where this measurement was possible, indicates decreased left atrial pressure and more nearly complete emptying of the left ventricle.

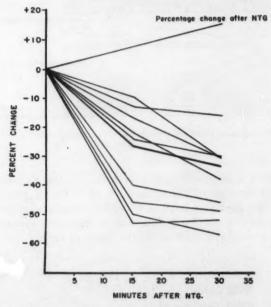


Fig. 3. Recent change in total pulmonary resistance 15 and 30 minutes following nitroglycerin administration (10 cases).

The percentage fall in mean pressure in the brachial artery was minimal as compared with the percentage fall in pressure in the pulmonary artery (table 2). Nitroglycerin and a ganglionic blocking agent such as hexamethonium had somewhat contrasting effects on the pressure in the pulmonary and brachial arteries (figure 4).

There was no consistent alteration in the cardiac output following nitroglycerin administration. In six of the cases the cardiac output was increased, and in seven the output was decreased during the first 15 minutes.

It is of interest that no significant increase in heart rate occurred following nitroglycerin administration. The maximal change in rate varied

between an increase of four beats per minute and a decrease of 10 beats per minute (a patient with transient complete heart block excluded). The change in heart rate was minimal whether the patient was on maintenance digitalis therapy or had not been digitalized. One of these patients was in chronic auricular fibrillation. In one of the patients, transient complete heart block developed during the study. Whether this was due to the effect of nitroglycerin or to the position of the catheter could not be determined.

One patient with a clinical diagnosis of angina pectoris was catheterized as a part of a preoperative study in preparation for pericardial poudrage. The clinical syndrome in this patient was typical and quite severe, with sudden onset of pain precipitated by slight exertion, with radiation into the

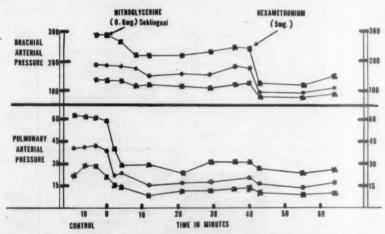


Fig. 4. Contrasting effect of nitroglycerin and hexamethonium on pulmonary artery and systemic hypertension.

left arm and immediately relieved by sublingual nitroglycerin. Catheterization and arterial cannulation were done with ease. When we were ready to do the initial control cardiac output, the patient developed a typical episode of severe anginal pain similar to that experienced on the wards. After assuring ourselves that this episode seemed no more severe than the usual ones, and that no abnormalities in cardiac rhythm had developed on the electrocardiogram monitor, we quickly obtained hemodynamic data on this patient during the height of the angina and following its relief by nitroglycerin. Figure 5 illustrates the hemodynamic data. A sharp rise in pulmonary artery pressure was observed with the onset of pain. The pulmonary and systemic arterial resistances were greatly increased. On administration of the sublingual nitroglycerin the pain rapidly disappeared and there was a concomitant precipitous drop in pulmonary arterial pressure and resistance. This patient showed prompt relief of angina pectoris on

the catheterization table as he had on the ward, and seemed to have no ill effect whatever from the experience.

It is to be noted that there were no significant untoward reactions in these cardiac patients following nitroglycerin administration.

SUMMARY AND CONCLUSIONS

1. The substernal distress associated with paroxysmal dyspnea of left heart failure is frequently of such severity as to be described by the patient as substernal pain. Our experience indicates that the administration of nitroglycerin (0.6 to 1.2 mg.) sublingually is often effective emergency therapy in the relief of this respiratory and retrosternal distress.

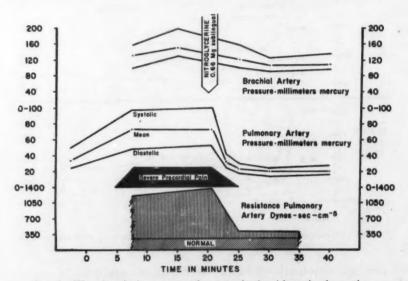


Fig. 5. Nitroglycerin in severe angina pectoris-hemodynamic observations.

2. As a result of these clinical observations a physiologic study using right heart catheterization was made in 13 patients with left heart failure to determine some of the hemodynamic effects of nitroglycerin administration.

3. In 10 of the 13 patients a prompt reduction in the pulmonary hypertension was observed following administration of nitroglycerin. In four cases where we were able to measure pulmonary wedge pressure, a significant fall in wedge pressure was also observed.

4. In 12 cases the total pulmonary resistance fell promptly during the first 15 minutes following nitroglycerin therapy. There was no consistent alteration in the cardiac output, nor was there a significant increase in heart rate.

5. One patient with coronary artery disease developed a typical episode of angina pectoris with radiation into the left arm similar to his well documented previous attacks during the period of control hemodynamic observations. During the height of precordial pain there was a sharp increase in the pulmonary artery pressure, and the pulmonary resistance was found to be greatly elevated. Nitroglycerin administration resulted in a prompt reduction of pulmonary artery pressure, total pulmonary resistance and complete disappearance of anginal pain. The patient had no subsequent complications as a result of this experience.

6. The clinical and physiologic data obtained after nitroglycerin administration suggest that this drug has an important place in the management of patients with pulmonary artery hypertension and paroxysmal dyspnea

associated with failure of the left ventricle.

SUMMARIO IN INTERLINGUA

Le disconforto retrosternal que es associate con le dyspnea paroxysmal de insufficientia sinistro-cardiac pote attinger un grado de severitate que le medico se senti justificate a proponer le erronee diagnose clinic de angina de pectore.

Patientes in nostre clinica cardiac ha frequentemente reportate le obtention de alleviamento del disconforto retrosternal e del sensation suffocatori in dyspnea paroxysmal post que illes habeva recipite un dose sublingual de nitroglycerina. Iste agente se provava le plus efficase mesura de urgentia que le patiente poteva effectuar a su domocilio. Le resultatos clinic induceva nos a interprender un evalutation del hemodynamica de nitroglycerina in administration sublingual in patientes con insufficientia sinistro-ventricular. Le studio esseva excutate per medio de catheterismo dextero-cardiac.

Hypertension pulmono-arterial esseva presente durante le periodo de controlo in omne le casos studiate. Elevate valores del pression pulmonar a cuneo esseva constatate in le sex casos in que iste mesuration esseva completate a bon successo.

Nitroglycerina esseva administrate in doses sublingual de 0.6 a 1.2 mg.

In 10 ex 13 patientes, un prompte decrescentia del hypertension pulmono-arterial esseva observate. In le quatro casos in que le repetition del essayage del pression pulmonar a cuneo esseva completate a bon successo, un grado significative de reduction de ille pression esseva constatate. In 12 ex 13 casos, un prompte reduction del total resistentia pulmono-vascular occurreva intra le prime 15 minutas post le administration de nitroglycerina. Nulle alteration regular del rendimento cardiac esseva notate; similemente nulle augmento regular in le frequentia cardiac e solmente un reduction minimal in le pression brachio-arterial.

Es reportate le experientia inusual del caso de un patiente con morbo de arteria coronari qui esseva evalutate per catheterismo dextero-cardiac in preparation pro un therapia de impulveration pericardial. Durante le catheterisation, le patiente disveloppava sever angina de pectore identic con illo experientiate previemente per le mesme patiente in le curso de su sojorno al hospital. Le pression pulmono-arterial e le total resistentia pulmono-vascular montava marcatemente durante que le angina de pectore esseva a su culmine. Le administration de nitroglycerina resultava in le complete disparition del angina de pectore. Simultaneemente il occurreva un elimination precipitose del hypertension pulmono-arterial e un reduction del total resistentia pulmono-vascular.

Le datos clinic e physiologic obtenite post administrationes de nitroglycerina suggere que iste droga ha un placia importante in le tractamento de patientes con

hypertension pulmono-arterial e dyspnea paroxysmal in association con insufficientia sinistro-ventricular.

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THE PROBLEM OF THE DIAGNOSIS OF GASTRIC LESIONS *

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THE present study was undertaken in an attempt to estimate the frequency with which the clinician is faced with the problem of a gastric lesion of questionable diagnosis. If the problem is approached purely from the standpoint of surgically proved malignancies, it does not assume its proper importance. In addition to the fungating lesions in which ulceration is not necessarily a prominent feature, there is a large group of nonfungating gastric ulcerations in which malignancy must be suspected. It is this latter group to which this paper will direct the major portion of its attention.

The case material in this study comprises approximately 1,250 gastric lesions that were treated on the Medical and Surgical Service of the Presbyterian Hospital in New York during the years 1939 through 1949. Of this total, 650 were proved to be gastric carcinomas and 600 were benign ulcers. The number of benign ulcers given is taken from Record Room diagnoses, many of which were not proved by operation and pathologic diagnosis. The figure of 600 is probably correct within less than 5%. Of the total 650 gastric carcinomas, 299 proved to be resectable, and of these, 149 were classified as lesions in which invasion was the prominent feature. The remainder of the 299 resectable lesions were of the fungating or mixed The resected specimens were classified according to the standards of Golden and Stout 1 as fungating, superficial spreading, penetrating, linitis plastica, and mixed or unclassifiable. Throughout this paper we use the term "fungating" to refer to Stout's classifications of fungating and mixed types of carcinoma, and we use the term "nonfungating" to mean the penetrating, linitis plastica and superficial spreading types of carcinoma and also the benign ulcerations.

FUNGATING AND MIXED LESIONS

While it is our main purpose to analyze the nonfungating lesions most carefully, because of the marked difficulty they present in differential diagnosis, it may be valuable for a moment to summarize our experience with the

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fungating and the mixed lesions. Here it might be assumed that the diagnosis should be readily apparent, but this is not always the case. As noted above, of the 650 gastric carcinomas, 299 were resectable, and of these, 150 fell into the fungating or mixed categories. Of this group, 19 were not diagnosed as carcinoma preoperatively. The x-ray interpretations in this group were as follows:

Pyloric obstruction	6
Lesser curvature ulcer	6
Large folds	2
No lesion	3
Gastritis	1
Polyp	1

Six of these carcinomas were in the fundus, a region notably difficult to examine radiologically.

The 351 unresectable carcinomas were diagnosed by local biopsy, but obviously afforded insufficient pathologic specimens to use for purposes of classification. In this group a surprisingly large total of 45 cases were not diagnosed preoperatively by x-ray as being carcinoma. This is one out of every eight cases. The following table summarizes the x-ray interpretation in this group:

Ulcer	11
Pyloric obstruction	10
No lesion	9
Antral gastritis	6
Large folds	3
No x-rays	6

Nonfungating Lesions

Turning now to the main theme, that of the predominantly ulcerating or invading lesion, we find the problem to be considerably more difficult. The magnitude of the problem of differential diagnosis in this group is, in our opinion, too often underemphasized, or is made to appear simpler than is actually the case. In spite of the rigid criteria which roentgenologists have set up for the diagnosis of the benign ulcer, the clinician realizes from his experience with individual cases which have proved to be the exception to the rule that no criteria are infallible. The same is true of gastroscopic and cytologic studies. The surgeon with the advantage of direct inspection cannot always be certain of his diagnosis, and even in the pathologic laboratory serial sections may have to be carefully studied before the presence or absence of cancer can be determined. For these reasons we have included the group of 600 ulcers that were eventually proved to be benign in the cate-

gory of lesions of questionable malignancy when they first confronted the clinician.

To demonstrate the frequency with which the surgeon is faced with a doubtful lesion on direct inspection, we have summarized in table 1 the surgeons' impressions at the operating table in 44 gastric carcinomas undiagnosed preoperatively by x-ray.

Table 1
25 Cases of Penetrating Gastric Carcinoma Undiagnosed Preoperatively

X-Ray Impression		Surgeon's Impres	sion
Ulcer	23	Ulcer	10
Obstructing lesion	2	Carcinoma	14
		Ouestionable	1

17 Cases of Superficial Spreading Carcinoma Undiagnosed Preoperatively

X-Ray Impr	ession	Surgeon's Impres	sion
Ulcer	13	Ulcer	11
Gastritis	3	Carcinoma	5
Normal	1	Questionable	1

In addition to the 42 cases given in table 1, there are two cases of linitis plastica not diagnosed by x-ray but recognized by the surgeon. It is thus apparent that in this group of questionable lesions the surgeon was able to recognize less than half by direct inspection. We have not recorded the number of times that the surgeon made a mistake in the other direction, that is, considered a benign ulcer to be malignant. Case 1, cited later, illustrates this type of error.

Of the total of 1,250 gastric lesions under consideration here, 708 (57%) presented a problem in diagnosis when originally seen. In the other 43% the diagnosis of carcinoma was obvious from the time the patient was first seen in the hospital. These figures are broken down in table 2.

Table 2
1250 Gastric Lesions, Prebyterian Hospital, New York, 1939–1949

	Diagnosis Apparent	Diagnosis Doubtful
Benign ulcers	0	600
Resectable penetrating, superficial spreading and linitis plastica carcinomas	105	44
Resectable fungating and mixed carcinomas	131	19
Unresectable carcinomas	306	45
Total	542 (43%)	708 (57%)

More detailed scrutiny of those cases of carcinoma that presented diagnostic difficulty reveals some interesting points. Among the total of 299 resectable carcinomas, 44 (15%) were nonfungating lesions in which the diagnosis was originally in question. The nonfungating carcinomas are summarized in table 3.

As illustrated in table 3, 14 of the 44 patients survived five or more years without recurrence, and 12 of these had tumors of the superficial spreading

Table 3

Resectable Nonfungating Carcinomas of Stomach, 1939–1949

Type of Carcinoma	Total Grou	p of Patients	Patients wit Diagnosi	h Preoperative s in Doubt
Type or Carcinoma	Number	5 Year Survivors	Number	5 Year Survivors
Penetrating Superficial spreading Linitis plastica	109 25 15	13 14 0	23 17 2	12 0
Totals	149	27 (18%)	44	14 (32%

type. This is a 32% five-year survival rate for this group, as compared with 18% in the total group of resectable carcinoma of the nonfungating type. This high survival rate results from the relatively large number of superficial spreading carcinomas in the doubtful group, since the five-year survival rate in this type of carcinoma in Harvey's study of resectable gastric carcinomas was 54%.² This relatively good prognosis in such penetrating earcinomas that preoperatively appear to be benign is one of the important reasons for establishing an early diagnosis whenever possible, and resorting to surgery in any ulcerating lesions that do not heal promptly and completely. Recently Runyeon and Hoerr also found the outlook for cure more favorable in this type of case, which they termed "masked malignancy." ⁶

CASE REPORTS

Three cases that illustrate difficulty in diagnosis are outlined below. They were selected to emphasize the importance of making an accurate diagnosis before resecting.

Case 1. The patient was a 71 year old male who complained of dull epigastric and left upper quadrant pain of two years' duration. His past history was irrelevant except for an epithelioma of the larynx, treated by radiotherapy. The onset of the pain was gradual, coming after meals and lasting one to two hours. It was accompanied by anorexia, and a gradual loss of weight from a maximum of 125 pounds to 86 pounds. There was only occasional vomiting, and no blood loss was recognized.

Physical examination revealed emaciation and evidence of generalized arteriosclerosis. The abdomen was free of masses or tenderness, but the liver was enlarged.

Significant abnormal laboratory findings were as follows: X-ray of the stomach revealed an ulcerating lesion of the pars media that was thought to be a carcinoma. Gastroscopy revealed a grayish nodular lesion of wide extent, thought to have the characteristics of malignancy. There was no free acid after histamine stimulation, and the electrogastrogram was said to be consistent with carcinoma. The surgeon's preoperative noted stated: "The case for carcinoma seems to be air-tight in this instance." The operative note states: "On the posterior surface of the lesser curvature in the mid-portion of the stomach was a mass 6 cm. in diameter which had apparently perforated into and invaded the middle portion of the body of the pancreas.

... It was felt that this lesion was in all probability malignant. . . ." A total gas-

trectomy was performed, with a subtotal pancreatectomy and splenectomy. The pathologic report was benign ulcer of the stomach.

The patient made a good recovery and maintained his weight and activity well until he died of recurrence of his laryngeal epithelioma 26 months after his gastrectomy.

Comment: In this instance the wrong operation was performed following an incorrect diagnosis, because the true diagnosis was not proved at operation.

Case 2. The patient was a 42 year old woman who complained of unrelenting epigastric pain for six weeks. It began suddenly and remained constant, without relation to meals. She vomited at least three times daily after onset; at times the vomitus was coffee-ground material. She developed watery diarrhea, severe anorexia and a distaste for food. She lost 17 pounds and became easily fatigued. There was no past history of digestive symptoms.

Physical examination revealed a pale, chronically ill woman without other posi-

tive findings except a blood pressure of 210/105 mm. of Hg.

Abnormal laboratory findings were: red blood cells, 4.1 million; hemoglobin, 9.7 mg.%; erythrocyte sedimentation rate, 65; no free hydrochloric acid in stomach after histamine stimulation. X-ray of the stomach showed that "a giant ulcer crater was present on the lesser curvature and posterior wall of the pars media." The x-ray report did not include an opinion as to whether the ulcer was malignant. The electrogastrogram indicated benign gastric disease. The clinical impression was "probable inoperable malignancy."

At operation a large mass was found involving the stomach, with many enlarged lymph nodes in the vicinity. Multiple biopsies taken of the large ulcer from inside the stomach revealed no evidence of malignancy. Had the mass been neoplastic instead of inflammatory, no resection would have been attempted. With the diagnosis of benign ulcer established, a partial gastrectomy could be done, cutting close to the margin of the ulcer and excising it. The patient's postoperative course has been uncomplicated.

Comment: In this case, the choice of the correct operation was possible only after the diagnosis was confirmed at operation.

Case 3. This 42 year old man, an immigrant, without previous symptoms, developed sudden left anterior chest pain that radiated to the left arm. This pain continued almost daily. He also developed sharp pain in the epigastrium that came on two hours after eating, was relieved by milk and food, and frequently wakened him at night. He was admitted to the Medical Service where, following tests that included gastrointestinal x-rays, a diagnosis of duodenal ulcer was made. No heart disease was demonstrated. The patient improved on a conservative ulcer regimen but had recurrence of epigastric pain after leaving the hospital and was re-admitted. His appetite had remained good, and he had lost only five pounds.

At the time of the second admission the physical examination was unrevealing. The only abnormal laboratory findings were: (1) the free acid after histamine was 73 units, total acid 96 units; (2) a second x-ray of the stomach suggested an ulcerating carcinoma on the lesser curvature, but a repeat study 10 days later showed a definite regression in the size of the ulcer crater without convincing evidence of filling defect, and the impression then was of a "healing benign gastric ulcer," although ulcerating carcinoma could not be completely excluded.

At operation the stomach was opened, revealing an ulcer that appeared to be

healing. Multiple biopsies which were taken of the ulcer were examined by quick frozen section and were said to be benign. A partial gastrectomy was done. The final pathologic diagnosis was carcinoma of the stomach, superficial spreading type. Review of the frozen section slides revealed that this diagnosis could have been correctly made before the extent of the operation was decided upon. Because it appeared that by good luck the resection had gone well wide of the tumor, and because the lymph nodes were not involved by tumor, no further surgery was done.

The patient has done well since operation, but it is too soon to tell whether his

carcinoma is arrested.

Comment: This case is an example of a carcinoma of a type that is favorable for cure but difficult to distinguish from benign ulcer. It illustrates that even the most reliable of differential diagnostic tests can be deceiving.

DISCUSSION

The foregoing statistics have been presented to emphasize the frequency with which the physician is faced with the diagnostic problem of differentiating a benign from a malignant gastric ulceration. We feel that every gastric ulceration must be treated as a potential malignancy. The fact that the resectability rate and the cure rate are relatively high in those ulcerating malignancies in which the diagnosis is originally in doubt makes this approach of utmost importance to the individual patient.

It is our belief that even in apparently benign gastric ulcerations that are treated conservatively, carefully repeated x-ray examinations are indicated to ascertain with the greatest possible certainty that the size of the ulcer is decreasing under treatment in both depth and transverse diameter. Ulcers that either fail to show clear evidence of healing by x-ray after three weeks of therapy or fail to heal completely in four to six weeks should be operated upon, even though it is well recognized that ulcers penetrating into the pancreas or surrounded by dense, poorly nourished reparative tissue often heal slowly. It is also important to prove that the ulcer remains healed. This is best done by repeat x-ray studies at approximately two, six and 12 months after the ulcer has apparently healed. When there are features that weigh in favor of a diagnosis of malignancy, either by x-ray or by gastroscopic or cytologic examinations, surgery is usually recommended without delay. Cytologic studies have not frequently been helpful in our hands, but a positive Papanicolaou smear is always a clinching argument in favor of malignancy, regardless of how rarely we have obtained this in the really difficult diagnostic situations. The persistent absence of free hydrochloric acid in a case of gastric ulceration is a strong indication for surgery, as is the location of an ulcer on the greater curvature of the stomach. It is our belief that the reappearance of a gastric ulcer that has healed also demands surgery. There are several reasons for this point of view. First, the recurrence of an ulcer once fully healed points to chronicity and a constitutional inherent weakness in this respect. Second, the risk of mistaking a malignant lesion for a benign one is even greater in a patient who has already

healed an ulcer, for this fact tends to give the physician an unwarranted sense of security. This aspect of the problem, i.e., how often a patient with a history of a healed benign ulcer eventually develops a gastric carcinoma, has generally defied statistical analysis. In an earlier study of this problem, using the case material of the Presbyterian Hospital, Flood and Hennig ^a reported a relatively small group (101 patients) with benign gastric ulcer followed over the years. In this group there was a surprisingly high incidence of five who eventually developed gastric carcinoma. Three of these malignancies were at the sites of the previously benign ulcers; the other two were in different parts of the stomach.

Another fact to be kept in mind in considering surgery for a patient with a benign ulcer is that the results of gastric resection for these lesions have been generally excellent, better than for duodenal ulcers.⁴ The average operative mortality in good hands is about 1%, recurrent or marginal ulcers are rare, and nutritional disturbances and dumping are infrequent, provided the surgeon does not remove more than about half of the stomach. It is not necessary to remove more than this amount of stomach, no matter how high the ulcer lies, provided it is shown at operation to be benign.⁵

SUMMARY

Of a total of 1,250 gastric lesions, there were 708 (57%) in which the diagnosis was originally in doubt. Those cases of resectable carcinoma that originally appeared to be benign ulcerations proved to have a better prognosis than the resectable carcinoma group as a whole. All available methods of diagnosis, including repeated x-ray examinations, gastroscopic and cytologic studies, and tests of free hydrochloric acid secretion, should be employed as needed in the study of an apparently benign ulcer under conservative medical management in order to minimize the risk of temporizing with a gastric carcinoma. It is believed that conservative management can be followed in selected patients with a minimal error, and that the risks of such an approach are not greater than the risks involved in following a policy of resecting all gastric ulcerations, especially if the resections are done without first proving the diagnosis. If any of the diagnostic studies weigh in favor of malignancy, and especially if healing is not prompt, complete and permanent, early surgery is usually warranted. It is difficult to state general rules that apply to all cases, because the associated circumstances and varied degree of suspicion of malignancy that apply to each case make it always an individual problem.

SUMMARIO IN INTERLINGUA

Iste studio de 1.250 lesiones gastric, tractate al Hospital Presbyterian de New York, esseva interprendite pro determinar le frequentia con que le clinico se trova confrontate con le problema de un lesion gastric de diagnose questionabile. Le serie include 650 carcinomas gastric. De istos, 299 esseva resectionabile. Inter iste 299,

un total de 150 representava le categorias fungisante o mixte, secundo le classification de Golden e Stout. Le 150 includeva 19 que non esseva diagnosticate como carcinoma ante le operation. Inter le 351 carcinomas non-resectionabile, 45 non esseva diagnosticate ante le operation.

Le problema del lesiones ulcerative se provava plus difficile. Le 600 ulceres que ultimemente esseva recognoscite como benigne es includite in le categoria de lesiones de malignitate questionabile al tempore del prime examine per le clinico. In plus, le serie total etiam includeva 105 resectionabile malignitates del classes penetrante e diffusori superficial e del classe de linitis plastic in que ulceration esseva un aspecto prominente. De istos, 44 non esseva diagnosticate ante le operation. Le diagnose esseva considerate como questionabile in un total de 708 casos, i.e. in 57% del serie complete de 1.250 lesiones gastric.

Es presentate reportos de casos individual pro illustrar le difficultate del diagnose de lesiones gastric, tanto ante le operation como etiam al tempore del operation quando le lesion es directemente exponite al vista del chirurgo. Le casos de carcinoma resectionabile que pareva originalmente esser ulcerationes benigne habeva un prognose plus favorabile que le gruppo de carcinomas resectionabile in su totalitate.

Es opinate que un tractamento conservative pote esser usate in seligite patientes con un margine minimal de error, providite que omne le cognoscite methodos diagnostic es empleate. Le risco inherente in iste attitude non es plus grande que le risco inherente in resectionar omne ulcerationes gastric. Si ulle del studios diagnostic—roentgenographia, gastroscopia, cytologia, etc.—supporta le suspicion de malignitate e specialmente si le resanation de un ulceration gastric non es prompte, complete, e permanente, le intervention chirurgic es usualmente indicate. Le importantia de sectiones congelate al tempore del operation es evalutate.

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THE INDICATIONS FOR SURGERY IN PULMONARY TUBERCULOSIS*

By JOHN D. STEELE, M.D., San Fernando, California

The use of antimicrobial agents has changed appreciably the role of surgery and also the choice of surgical procedures in the treatment of pulmonary tuberculosis. Because antimicrobial agents alone control many lesions, some of the less effective surgical and collapse procedures have been discarded, whereas others have become more effective when used in conjunction with chemotherapy. Concomitant improvements in surgical technic have also contributed to the change.

It is interesting to compare the various methods used in the treatment of pulmonary tuberculosis 20 years ago with those in use today. Twenty years ago, strict bed-rest was the foundation for all other forms of treatment, whereas today the use of bed-rest has been considerably modified, and antimicrobial therapy is most certainly fundamental. Pneumothorax has been discarded, at least in this country. The use of pneumoperitoneum has been discontinued by many but is still used to some extent by others. Twenty years ago, pulmonary resection was used only as a last resort, but today, pulmonary resection is the first choice when surgery is indicated.

In general, surgery is indicated in the treatment of pulmonary tuberculosis either when antimicrobial therapy has failed to close cavities or in the case of fibrocaseous residuals when it is believed they are dangerous as far as relapse is concerned.

Cavitary lesions will be considered first. It has been shown that, in large series of patients having one or more cavities at the start of chemotherapy, closure can be achieved after eight months of chemotherapy in less than 40%, and after 12 months of therapy in only about 50%. As might be expected, small cavities respond better than large ones. A change in chemotherapy has little effect on previously unclosed cavities.¹⁻³

In so-called "open positive" cases in which cavities remain unclosed and pulmonary secretions remain positive for tubercle bacilli in spite of adequate courses of antimicrobial therapy, surgery offers the only hope of controlling the disease (figures 1 and 2). The risk of resectional surgery in such patients is definitely greater than in those whose tubercle bacilli have been suppressed sufficiently to produce "conversion" of the sputum. The risk of resection is greatest in patients whose tubercle bacilli have lost suscepti-

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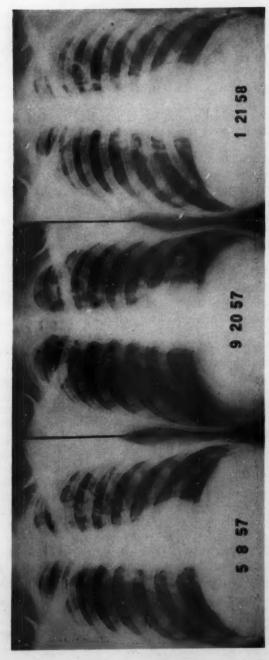


Fig. 1. Case 1. Negro male, age 27, whose tuberculosis was first discovered in March, 1957. In spite of a 10-month course of SM, INH and PAS, the cavity in the left upper lobe remained unclosed and sputum remained positive for tubercle bacilli. A left upper lobectomy was performed. The resected specimen contained a 6 cm. cavity lined with shagey, necrotic material. (left) Roeintgenogram taken a few weeks after start of chemotherapy. Large cavity present in left upper lobe. (right) Roeintgenogram 10 months after start of chemotherapy. Large cavity present in left upper lobe.

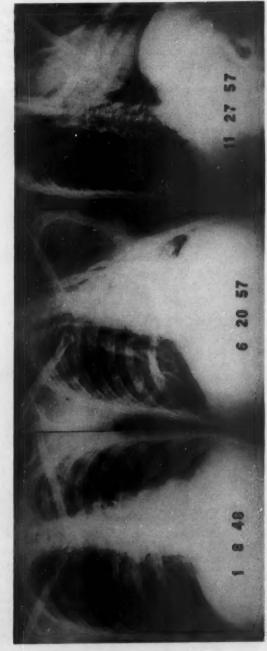


Fig. 2. Case 2. White male, age 36, who had had tuberculosis since 1947, when a right pneumothorax was induced. This was continued for two years. A left thoracoplasty was performed in 1949. A left phrenic paralysis was done in 1956. In spite of these measures and multiple courses of antimicrobial therapy over the 10-year period, his sputum remained persistently positive and his tubercle bacilli became resistant to SM and INH. A left pneumonectomy was performed and a "destroyed lung" found containing an irregular 15 mm. cavity, brondinar dilatation and thickening, multiple areas of nodular tuberculosis. (left) Roentgenogram in 1948, showing the right pneumonectory areas of cavitation at left apex. (center) Roentgenogram showing residual fibrotic disease on right and thoracoplasty on left (right) Bronchogram showing dilated bronchial tree on left beneath thoracoplasty.

bility to potent antimicrobial agents.^{8, 4} In many instances, the loss of susceptibility is due to a lack of coöperation on the part of the patient, but in others it may be due to extended expectant treatment with chemotherapy in the face of a persistent cavity. In localized, unilateral cavitary disease, development of resistance can frequently be avoided by anticipating the limita-

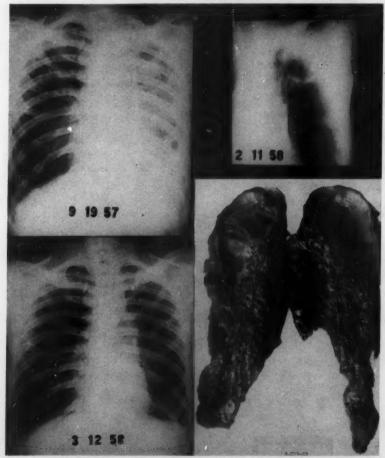


Fig. 3. Case 3. Negro male, age 32. SM, INH and PAS started in July, 1957. Sputum promptly became negative on culture for tubercle bacilli but large cavity persisted at left apex. (upper left) Roentgenogram taken a few weeks after start of chemotherapy, showing bilateral exudative pulmonary tuberculosis, predominant on left. (upper right) Sectional radiogram of apex of left lung, showing cavity persisting more than six months after start of chemotherapy. (lower left) Preoperative roentgenogram. Cavity at left apex less clearly seen than in preceding roentgenogram. (lower right) Resected left upper lobe. The large cavity was lined with cells resembling atrophic bronchial epithelium except for two small ulcerated areas, which are seen in cavity wall on right side of specimen. Microscopically, these were caseous nodules ulcerating into the cavity.

tions of chemotherapy as far as cavity closure is concerned, and performing surgery, when feasible, approximately six months after starting therapy.

Conversion of pulmonary secretions during the chemotherapy occurs much more frequently than does cavity closure, leaving a large group of patients with so-called "open negative" lesions (figure 3). Although a relatively small percentage of these cavities will show no evidence of active infection when removed, most of them are not healed, and the relapse rate in this group is known to be high.^{3, 5, 6, 7} Furthermore, it is impossible by roentgenographic examination to determine when a cavity might actually be healed, so that in all such "open negative" cases surgery is advisable unless there is a strong contraindication.

In discussing the indications for surgery for residual, stable, fibrocaseous lesions in patients who have been treated with chemotherapy, we must remember that long-term antimicrobial therapy, measured in terms of years, has been in general use for only about five years. For this reason we do not yet know exactly what to expect as far as eventual reactivation of these lesions is concerned. Thus there is still much controversy as to the indications for resection of some of these closed necrotic foci.

Table 1
Indications for Resection of "Closed Lesions" in 38 VA-Armed Forces Hospitals

Special indications (youth, relapse, etc.)	15
3.0 cm. or over	1
2.5 cm. or over	1
2.0 cm or over	10
1.5 cm. or over	1
1.0 cm. or over	4
Cavities filling on chemotherapy	4
Do not resect	1
"When seen by x-ray"	1

Varying indications for the resection of these lesions are well illustrated in table 1, compiled from a questionnaire recently sent to a group of VA-Armed Forces hospitals.⁸ It will be noted that the indications vary widely and that the frequency of resection increases with the size of the lesion. Most use special indications, such as youth, previous instability of the lesion (figure 4), and social indications, such as the inability of a patient to lead a restricted life.⁹ Many of the closed lesions can be removed by segmental or subsegmental resection without sacrificing an appreciable amount of lung tissue, which at times tends to make resection attractive to the physician and the patient.

As to the surgical procedures used for the general types of lesions mentioned above, pulmonary resection, when feasible, is the operation of choice in the surgical treatment of pulmonary tuberculosis. The extent of resection may vary all the way from a small subsegment up to an entire lung. A rough indication of the safety of pulmonary resection for tuberculosis is given in table 2, covering 6,290 resections performed in the VA-Armed Forces

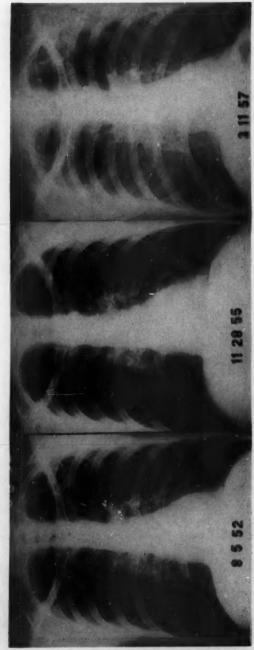


Fig. 4. Case 4. Roentgenogram and surgical specimen of a 37 year old white male whose tuberculosis apparently responded satisfactorily to chemotherapy courses in 1952 and 1953. Gastric resection was performed in 1956, and a reactivation of the tuberculosis was discovered a year later. The lesion again regressed on an eight-month retreatment course of antimicrobial therapy, following which a segmental resection showing repression of lesion at left apex following initial course of chemotherapy. (right) Roentgenogram showing reactivation of left apical lesion.

hospitals from 1952 to 1957.¹⁰ All had antimicrobial drug coverage of varying duration. This series contains an appreciable number of "salvage" cases. This is one reason for the high mortality rate for pneumonectomy, which, incidently, was reduced to 5% in the last two years of this period, during which possibly more favorable cases were seen. The rates for the other types of resections remained relatively constant for the five-year period.

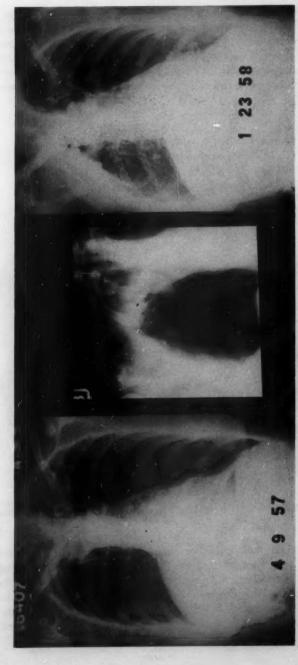
Table 2
Surgical Mortality, 6,290 Pulmonary Resections for Tuberculosis, VA-Armed Forces Hospitals, July 1, 1952, to July 1, 1957

Procedure	Operations	Deaths	Per Cent
Pneumonectomy	330	41	12.0
Lobectomy	2362	65	2.7
Segmental	2775	26	0.9
Subsegmental	794	0	-



Fig. 4 continued. Resected apical-posterior segment of left upper lobe. The necrotic foci yielded tubercle bacilli on culture. (There had been no history of a positive sputum or gastric specimen.)

When resection is undesirable or unduly risky because of extensive disease, bacillary resistance or low respiratory reserve, surgical collapse therapy measures (standard thoracoplasty and extraperiosteal plombage thoracoplasty) may be used (figures 5 and 6). Because collapse procedures are used frequently in these salvage situations, the therapeutic results in general are poorer than are those of resection. In some cases regarded as poor risks collapse can be given a trial before resorting to resection.



Fro. 5. Case 5. The use of standard thoracoplasty to control the disease of a 56 year old white female who had had tuberculosis for over 20 years. Her sputum was positive. On bronchoscopy there was a marked bronchial obstruction on the right due to previous bronchial tuberculosis. It was considered that thoracoplasty was a far safer procedure than resection in this case. (left) Preoperative roentgenogram. A small cavity is present at right apex. Elevation of right hemidiaphragm was produced by previous therapeutic paralysis of phrenic nerve. (center) Sectional radiogram showing cavity more clearly than in preceding roentgenogram. (right) Roentgenogram following selective sixrib right thoracoplasty.

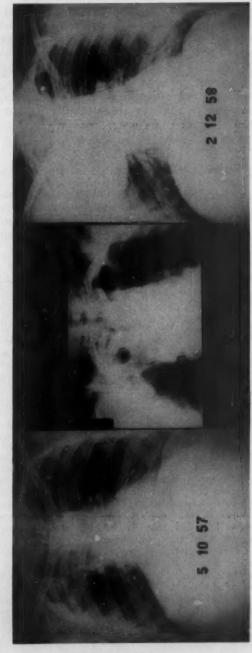


Fig. 6. Case 6. Extraperiosteal plombage with paraffin filling used to control the disease of a 27 year old psychotic male who had had tuberculosis for four years and a spread in 1954 while on antimicrobial therapy. His sputum had remained positive and a cavity had persisted at the right apex Collapse was chosen because a pneumonectomy would have been necessary if resection had been performed. The sputum is now negative. (ieth Properative roenigenogram showing extensive disease on right. (center) Cavity at right apex well demonstrated on sectional radiogram. (right) Prostoperative roentgenogram showing density produced by the extraperiosteal paraffin filling on right.

Plombage thoracoplasty has certain advantages over standard thoracoplasty in that it is a one-stage procedure and usually is tolerated better by patients who are poor risks with low respiratory reserves. However, this procedure is less effective than standard thoracoplasty for the closure of large or mesially placed cavities. Furthermore, there is the potential danger, even though slight, of late infection in the extraperiosteal space, where various foreign bodies, such as lucite spheres, polythene packing, ivalon sponges and paraffin, are used to fill the space between the ribs and the lung. For this reason, consideration must be given, at least in young patients, to an additional operation for the removal of the plombe.

SUMMARY AND CONCLUSIONS

The indications for surgery in pulmonary tuberculosis have become better established during the last five years as the potentialities and limitations of antimicrobial therapy for the disease have become better understood.

Pulmonary resection is the most widely used surgical procedure. It is generally agreed that cavitary lesions which have not closed after a reasonable trial of chemotherapy should be resected when possible. The resection of stable, residual, fibrocaseous lesions is a more controversial subject.

Surgical collapse therapy (standard or plombage thoracoplasty) may be preferable to resection in certain patients who are poor risks for resection either because of loss of sensitivity of organisms to potent antimicrobial agents or because of considerable reduction in respiratory reserve due to extensive disease.

Although the immediate results of most surgical procedures are well known, the evaluation of long-range results will have to await the results of future follow-up studies.

SUMMARIO IN INTERLINGUA

Le uso de agentes antimicrobial ha notabilemente alterate le rolo del chirurgia e le selection del manovras chirurgic in le tractamento de tuberculose pulmonar. A causa del facto que agentes antimicrobial per se es capace a disponer de multe lesiones, alicunes del minus efficace manovras chirurgic e technicas de collapso ha essite abandonate, sed alteres ha devenite plus efficace per lor uso in conjunction con mesuras chimotherapeutic. Importante meliorationes del technica chirurgic ha etiam contribuite a iste disveloppamento. Vinti annos retro, resection pulmonar esseva usate exclusivemente como mesura del "ultime spero." Hodie illo es le operation del prime election quando un intervention chirurgic es indicate.

In general, chirurgia es indicate in le tractamento de tuberculose pulmonar (1) quando le therapia antimicrobial non succede a clauder le cavitates o (2) in le caso de residue lesiones fibrocasee quando istos pare esser periculose con respecto al occurrentia possibile de un recidiva.

In casos del typo designate como "aperte positive," in que il ha persistentia de non-claudite cavitates e in que le secretiones pulmonar remane positive pro bacillos de tuberculose in despecto de adequate cursos de therapia antimicrobial, le intervention chirurgic offere le sol spero pro vincer le morbo. Resection es etiam indicate definitemente in lesiones "aperte negative" (con presentia de cavitates aperte e sputo negative), proque un ver sanation de tal lesiones es relativemente rar.

Therapia a collapso (del typo standard o thoracoplastia a plombage) es forsan a preferer al resection in certe patientes qui non es bon candidatos pro le resection a causa del presentia de organismos que ha perdite lor sensibilitate al effecto de potente agentes antimicrobial o a causa del facto que illes ha suffrite un considerabile reduction de lor reserva respiratori in consequentia del grande extension del morbo.

Ben que le resultatos immediate de quasi omne le manovras chirurgic es ben cognoscite, le evalutation del resultatos a longe vista debe attender le conclusiones de futur studios de consecution.

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INCREASING CLINICAL SIGNIFICANCE OF ALTER-ATIONS IN ENZYMES OF BODY FLUIDS*

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INTRODUCTION

An inestimable wealth of biochemical information dealing with the measurement, characterization and distribution of tissue enzymes has accrued over the years. These archives include studies of crystalline enzymes derived from liver, muscle and other animal tissues, enzyme activities of tissue homogenates, intracellular enzyme localization by histochemical technics, and enzymatic patterns in the cellular and other components of body fluids. Although for some time medical science has put to clinical use basic enzyme information dealing with alkaline and acid phosphatase,1,2,3 amylase,* lipase * and thrombin, 5 recent years have seen an increasing tendency to translate fundamental enzyme knowledge into clinical tools for the definition, study, diagnosis and treatment of disease. In some instances, pathologic states have been explained etiologically in light of enzymatic defects; wholly or in part, enzymatic defects account for constitutional hyperbilirubinemia,6 congenital galactosemia,7 phenylketonuria,8 hypophosphatasia9 and other disease states. The investigation of some drug-induced anemias, 10 myelogenous leukemia 11 and other pathologic states has included enzyme studies of leukocytes, erythrocytes and platelets 12 of the blood. The diagnosis of myocardial infarction,13 disseminated cancer,14 hepatitis 15 and other diseases has been facilitated by the measurement of enzyme changes in the serum and plasma. The therapeutic use of enzymes in the management of empyema,16 thrombophlebitis,17 arterial emboli,17,18 renal calculi 19 and inflammatory arthritis 16 has received increasing attention.

It is the purpose of this presentation to discuss the increasing clinical importance of the aspect of clinical enzymology dealing with the use of body fluid enzyme alterations in the diagnosis of disease. The material discussed will be concerned with a selected group of the more recently introduced measurements of enzyme activities of the noncellular components of serum, plasma, cerebrospinal fluid and serous effusions as these body fluid enzyme alterations pertain to cardiology, gastroenterology, neurology and oncology.

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No attempt will be made to review completely the increasingly large experience and literature in this field of clinical enzymology.

GASTROENTEROLOGY

The laboratory diagnosis of pancreatic disease has depended in part on the finding of increased serum amylase and lipase.⁴ Recent use has been made of the antithrombin titer, although further clarification of the trypsin-antithrombin relationship is needed before this plasma determination can be applied as a pancreatic function test. Provocative pancreatic enzyme tests have been suggested using parasympathomimetic agents, secretin and opiates to elicit characteristic serum amylase and lipase alterations and plasma antithrombin titers.⁴ Extension of enzyme reflections of pancreatic disease have been made by measuring urinary lipase and amylase. Recent observations have dealt with the question of the mechanism involved in the

Table 1

Distribution Among the Globulin Fractions of Serum of Activity of Four Serum Enzymes

Y. W., Q, 60 yrs., adenocarcinoma of breast with hepatic metastases

Serum Globulin -		Enzyme Activity	y (Per Cent of Total)	
Component -	GO-T	GP-T	Lactic Dehydrogenase	Glutathione Reductase
γβ	33 52	47	26 30 22	75 25
α	15	53	21	
Total enzyme activity per ml. serum (in units)	276	40	1.000	250

elevation of serum enzymes during the course of pancreatic disease, and have suggested that, in part at least, the elevation of serum amylase is a result of the release of ACTH and activation of the adrenal cortex.²⁰

The study and diagnosis of liver and biliary tract disease have made increasing use of serum enzyme alterations.²¹ Measurement of serum enzymes is in one sense an extension of the accepted clinical usefulness of estimation of serum proteins. Inasmuch as most serum enzyme activities are reflections of minute components of the various globulin constituents of serum proteins ²² (table 1), measurement of serum enzymes may be considered as a further refinement and detailing of the subtle serum globulin alterations associated with various disease states (figure 1). These serum enzyme changes, in addition to reflecting serum globulin changes, are composite expressions of such other factors as enzyme inhibitors, activators, anti-

TABLE 2

Comparison of the Activity of Four Serum Enzymes and the Electrophoretic Composition of Serum Protein Observed in Normal Individuals and in Patients with Hepatitis and Various Other Disease States

Serum enzymes are components of globulin fractions, although serum globulin alterations are not necessarily accompanied by serum enzyme changes. Contrariwise, serum enzyme activities may increase in the absence of apparent changes in the electrophoretic pattern of serum proteins.

			Serum P	Serum Paper Electrophoretic Pattern (gm. %)	rophoretic %)	Pattern			Š	Serum Enzymes (units/ml.)	168	
Patient Designa- tion	Clinical Diagnosis	Total Protein	Albumin	la la	a2 .	00.	*	Alkaline Phospha- tase	Glutamic Oxalo- acetic Trans- aminase	Glutamic Pyruvic Trans- aminase	Lactic Dehydro- genase	Gluta- thione Reduc- tase
	Normal values	6.5 to 7.9	3.75 to 5.23	0.13 to 0.29	0.31 to 0.89	0.48 to 1.06	0.63 to 1.77	1.5 to 4.0	8 of 4	5 to 35	to 500	10 00
HOWOH O'N'N'N	Normal individual Normal individual Normal individual Normal individual Normal individual	7.1	4.56 4.30 4.85 3.80 3.48	0.24 0.23 0.28 0.28 0.40	0.51 0.47 0.88 0.58 0.89	1.06 1.04 1.06 1.48	1.24 1.06 0.91 1.23 1.45	3.0 3.4 3.4 3.2	38 14 18 8 8 8	20 112 112 28 28	280 200 300 240 300	442332
E. A.	Homologous serum hepatitis Homologous serum hepatitis	4:7. 6:7. 8:7. 8:7.	3.90 3.80 4.65 2.72 3.50	0.37 0.23 0.43 0.39	0.05 0.85 0.92 0.91	0.92	1.58 1.48 1.10 1.77 1.70	10.1 7.3 1.6 16.5 6.5	840 149 13 68 68 24	1,200 240 240 260 34 34	360 360 380 380 380 380	40 37 32 32
M. J.	Homologous serum hepatitis, su acute	sub- 7.8 7.1 7.1 7.1	3.45 3.45 3.45	0.32 0.35 0.36 0.33	0.69 0.69 0.77 0.77	1.04	1.36 0.90 1.56 1.51	4.7 1.9 8.6 10.2 7.3	14 14 80 77	26 16 16 133 141		30 334

Table 2—(Continued)

			Serum P	aper Electi (gm.	Serum Paper Electrophoretic Pattern (gm. %)	Pattern			3.	Serum Enzymes (units/ml.)	les	
Patient Designa- tion	Clinical Diagnosis	Total Protein	Albumin	al	a2	•	*	Alkaline Phospha- tase	Glutamic Oxalo- acetic Trans- aminase	Glutamic Pyruvic Trans- aminase	Lactic Dehydro- genase	Gluta- thione Reduc- tase
M. A.	Homologous serum hepatitis and metastatic adenocarcinoma to liver	7.7	3.26	0.41	1.09	1.42	1.86	6.0	590	480	1,200	089
I. F.	Homologous serum hepatitis, Gaucher's disease	80.00	3.81	0.29	0.55	1.23	2.92	4.5	120	144	280	51
A. O.	Infectious hepatitis and cirrhotic and malarial hepatomegaly	8.4	3.72	0.41	0.56	1.51	3.03	9.7	2,300	820		8
V P	honotitie	8.0	4.20	0.21	0.54	1.04	2.01	3.3	388	400	460	40
		7.2	3.75	0.27	0.57	0.85	1.76	2.0	20	107	320	
		7.5	3.47	0.40	0.68	1.20	2.00	0.4	75	986	240	20
		7.4	3.77	0.25	0.37	1.25	1.76	3.3	64	72	330	30
		7.9	4.19	0.36	0.81	0.80	1.75	3.1	48	69	300	
		7.1	2.67	0.36	0.52	1.62	1.93	3.0	147	189	240	26
		6.9	2.45	0.41	0.74	1.54	1.76	3.2	141	176	300	
		7.1	3.47	0.25	0.53	0.97	1.88	3.4	112	107	160	34
A. W.	Homologous serum hepatitis,	7.5	2.67	0.40	0.54	1.46	2.45	0.00	516	344	440	32
	DOCCE S SALCOIA	7.6	3.75	0.38	0.70	1.50	1.27	0.0	16	12	260	100
Y. W.	Adenocarcinoma of breast with	7.6	3.04	0.44	0.68	0.72	2.74	9.5	216	32	1,200	192
* 327	hepatic metastases	15.3	4.04	1.00	1.21	2.58	6.48	12.6	195	20	1000	360
N. W.	Lymphosarcoma	4.0	3.07	0.30	0.44	1.42	1.45	2.00	30	36.	1,900	2002
VF	Active cirrhosis	7.0	3.74	0.37	0.85	1.23	1.73	3.4	96	11	400	200
F. W.	Hodgkin's paragranuloma	7.3	3.84	0.36	0.53	0.88	1.69	3.0	17	20	200	
R. S.	Boeck's sarcoid	7.9	2.60	0.43	0.62	1.28	2.98	3.3	80	96	400	
5.00	Lymphosarcoma with hemolytic	7.7	3,38	0.35	1.02	1.57	1.38	2.0	32	20	480	20

TABLE 2—(Continued)

			Serum P	aper Elect (gm.	Serum Paper Electrophoretic Pattern (gm. %)	Pattern			S	Serum Enzymes (units/ml.)	ıes	
Patient Designa- tion	Clinical Diagnosis	Total Protein	Albumin	al	α2	Ø.	*	Alkaline Phospha- tase	Glutamic Oxalo- acetic Trans- aminase	Glutamic Trans- aminase	Lactic Dehydro-	Gluta- thione Reduc- tase
D. S.	Inactive early latent syphilis	7.7	4.27	0.19	0.61	1.08	1.55	2.4	30	22		
		8.1	4.78	0.29	0.67	0.93	1.43	2.6	32	20	200	
M. J.	Infectious mononucleosis	8.3	4.01	0.47	0.81	1.33	1.69	2.5	20	16	160	
. H.	Miliary granuloma (cause unknown)	8.0	3.07	0.51	1.14	1.29	1.99	3.0	45	53	360	40
	of liver	7.6	3.36	0.41	1.04	1.29	1.51	3.4	40	45	460	28
	Acute leukemia	11.0	4.69	0	1.62	1.26	3.43	5.0	72	53	1,700	
Z. L. B.	Sickle-cell anemia	8.3	4.0	0.38	0.88	1.41	1.63		12	18	540	37
. D.	Myocardial infarction	7.1	3.17	0.37	1.08	1.52	96.0		06	30	800	40
		7.1	3.84	0.31	0.84	1.31	0.80		24	38	400	32
C. C.	Malabsorption (small bowel) syn-	8.1	4.29	0.36	0.74	1.17	1.54	2.0	22	24	480	
	drome	11.8	5.14	0.46	1.29	2.37	2.55	2.4	16	20	240	20
M. D.	Periodic (febrile) disease	7.7	3.85	0.37	1.15	1.14	1.14	3.0	24	20	200	24
· · ·	Pernicious anemia and hypoglo-	6.1*	3.40	0.37	0.55	1.83	0.0	2.0	27	20	180	
	bulinemia	6.0	3.12	0.36	69.0	1.14	0.67		25	13		
		5.5+	3.48	0.32	0.42	0.70	0.58		14	10	260	
		7.5+	3.55	0.46	0.87	1.54	1.08	2.4	18	15	260	26
1		5.6‡	3.02	0.35	0.36	1.17	0.71		18	14	250	30
P. M.	Chronic myelogenous leukemia	6.4	3.40	0.48	1 20	0.84	0.40	00	36	18	096	

* Before treatment with vitamin B₁₃.
† During treatment with vitamin B₁₂.
‡ Treatment with vitamin B₁₃ discontinued.

enzymes and other factors. For these and other reasons, activity alterations may not necessarily be correlated with the electrophoretic composition of the serum globulin (table 2). The serum enzymes recently introduced into the clinical armamentarium for the diagnosis of liver, biliary tract and pancreatic disease include isocitric dehydrogenase, ²³ 6-phosphogluconic dehydrogenase, ²³ glutamic-oxaloacetic transaminase (GO-T), ^{21, 24} glutamic-pyruvic transaminase (GP-T), ²⁴ hexose isomerase, ²⁵ cholinesterase, ²⁶ lactic dehydrogenase (LD), ¹⁴ ceruloplasmin, ²⁷ 5-nucleotidase, ²⁸ make dehydrogenase, ²⁹ trypsin ³⁰ and aminotripeptidase. ³¹ Serum isocitric dehydrogenase has been found to be of value in following the course of viral hepatitis. Limited experience with serum 5-nucleotidase suggests that this serum

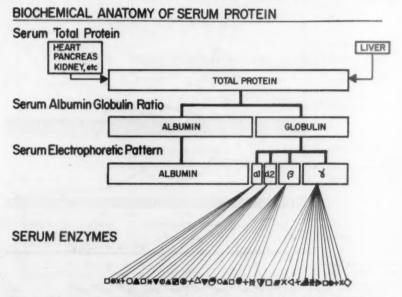


Fig. 1. Diagram of some of the constituents of serum protein. Serum enzymes are components of the various globulin fractions.

enzyme is as sensitive as is nonspecific alkaline phosphatase in detecting the presence of biliary tract obstruction, and is more selective because the serum enzyme activity is not increased in diseases of bone associated with osteoblastic activity. The reported experience with aminotripeptidase and 6-phosphogluconic dehydrogenase is too sparse to formulate any conclusions about the clinical applicability of these two parameters. Serum lactic dehydrogenase is of little use in the clinical appraisal of hepatic disease, whereas diminished serum ceruloplasmin is observed primarily in liver disease accompanying Wilson's disease. The two serum transaminase activities have found increasing acceptance as a means of evaluating liver and extrahepatic

biliary tract disease, and when these serum enzyme alterations, along with those of serum alkaline (SAL) phosphatase, are related to various hepatic and biliary tract diseases, patterns of serum enzyme changes emerge which are useful diagnostic laboratory adjuncts.

In most instances of extrahepatic biliary tract obstruction the serum transaminase values are elevated; SGP-T has been noted to be increased to

RK, 64, 9, EXTRAHEPATIC BILIARY OBSTRUCTION DUE TO HEAD OF PANCREAS ADENOCARCINOMA

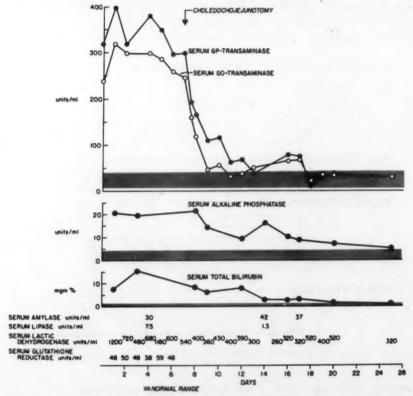
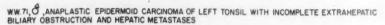


Fig. 2. Serial alterations of several serum enzyme activities and serum bilirubin observed in a patient with extrahepatic biliary tract obstruction due to adenocarcinoma of pancreas.

levels up to 400 units, with SGP-T greater than the SGO-T activity unless there is concomitant intrahepatic disease, in which instance the two transaminase activities approximated each other. Figures 2 and 3 summarize the serum enzyme alterations and other laboratory parameters in two patients with extrahepatic biliary tract obstruction due to carcinoma. The experience with transient, incomplete biliary tract obstruction without jaundice

has been limited, but it seems that any degree of extrahepatic biliary tract obstruction which fails to elevate serum bilirubin above the normal range will not significantly influence the levels of serum enzymes. The exceptions observed are in instances of acute necrotizing pancreatitis where the serum bilirubin remained within the normal range and where elevation in SGO-T



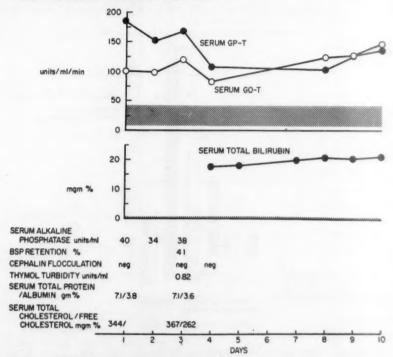


Fig. 3. Serial alterations of serum transaminase activities and other laboratory parameters in a patient with incomplete extrahepatic biliary tract obstruction and intrahepatic metastases from epidermoid carcinoma of the tonsil. The changing relationship of SGP-T to SGO-T activities reflects the summation of effects from the incomplete extrahepatic biliary tract obstruction and the intrahepatic metastatic deposits.

is presumably due to liberation of glutamic-oxaloacetic transaminase from necrotic pancreatic tissue.

Intrahepatic carcinoma or lymphoma associated with hyperbilirubinemia has been observed to be accompanied by marked elevations in SAL phosphatase. In some instances the SAL phosphatase presumably reflects osteoblastic lesions as well as hepatic metastases. In cases of jaundice due to intrahepatic malignant disease, serum transaminase values are above normal,

and in most instances SGO-T elevation is greater than that of SGP-T. Figure 4 diagrammatically summarizes the observations in a group of patients in regard to bilirubinemia and serum enzymes associated with intrahepatic primary or metastatic carcinoma or lymphoma. Figure 5 presents the laboratory findings in a patient with intrahepatic and extrahepatic reticulum cell sarcoma. During the first 45 days of observation the primary cause for the jaundice was common duct obstruction reflected in elevated SAL phosphatase and increased SGP-T and SGO-T, with SGP-T greater than SGO-T activity. With surgical relief of extrahepatic obstruction

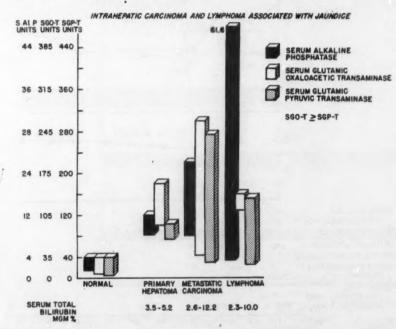


Fig. 4. Diagram of the range of change of three serum enzymes and serum bilirubin in a group of patients with intrahepatic carcinoma and lymphoma associated with jaundice.

and radiation treatment to the remaining enlarged nodes near the porta hepatis, SAL phosphatase fell toward the normal range and the activity of SGO-T became greater than that of SGP-T. The increasing jaundice and residual abnormal serum transaminase reflected primarily intrahepatic reticulum cell sarcoma.

In the absence of hyperbilirubinemia, intrahepatic lymphoma or leukemia may result in increased serum enzymes, but this is infrequent. When serum transaminase activities are increased by intrahepatic metastatic carcinoma, SGO-T is usually elevated to greater levels than is SGP-T, and the elevation appears to be directly related to the number of metastatic lesions and the

rapidity of growth of the metastases. Normal serum enzyme activity is consistent with the clinical conclusion of metastatic liver disease in the absence of hyperbilirubinemia. It seems that metastatic liver disease is reflected most accurately by increased bromsulfalein retention, increased SAL phosphatase, SGO-T, and SGP-T activities.

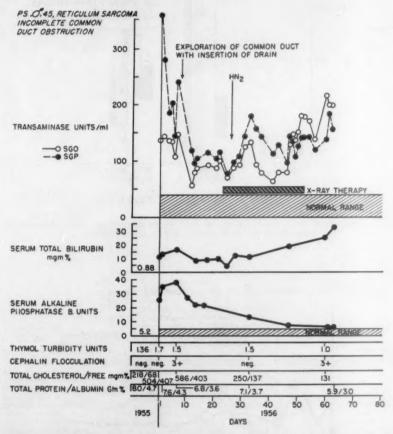


Fig. 5. Serial alterations of three serum enzymes and other laboratory parameters observed in a patient with reticulum cell sarcoma. As the extrahepatic component of the tumor responded to radiation therapy, the extrahepatic biliary tract obstruction cleared, resulting in a fall in serum alkaline phosphatase activity and a reversal in quantitative relationship of SGP-T to SGO-T activity.

Laennec's cirrhosis, when accompanied by hyperbilirubinemia, is associated with abnormal SGO-T which is greater than SGP-T activity. Figure 6 diagrammatically summarizes the observations in regard to bilirubinemia and serum enzymes in a group of patients with active Laennec's and post-

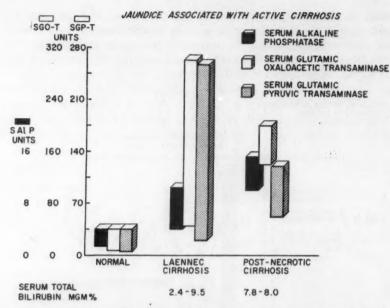


Fig. 6. Diagram of the range of change of three serum enzymes and serum bilirubin in a group of patients with jaundice due to active cirrhosis.

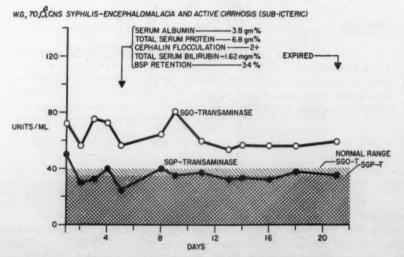


Fig. 7. Serum transaminase activities and other laboratory parameters observed in a patient with active Laennec's cirrhosis.

necrotic cirrhosis. Anicteric or subicteric patients with clinically active or progressive cirrhosis have increased SGO-T with normal or slightly increased SGP-T activity, the latter elevated to a lesser extent than the former. Figure 7 presents the laboratory findings in a patient with active Laennec's cirrhosis confirmed at postmortem examination.

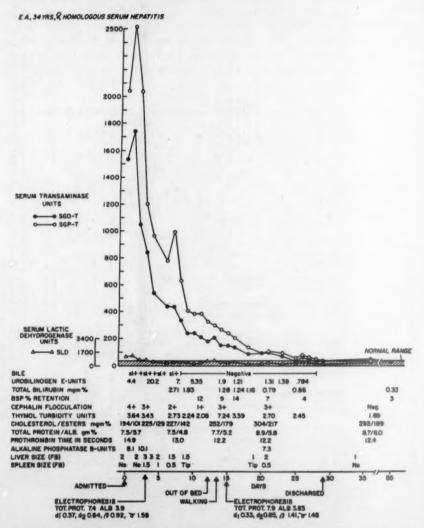


Fig. 8. Serial serum transaminase activities and other laboratory and clinical parameters observed in a patient with homologous serum hepatitis. Throughout the clinical course, SGP-T is greater than SGO-T activity.

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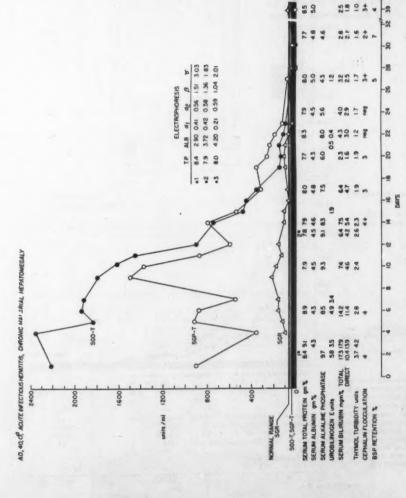


Fig. 9. Serial serum transaminase activities and other laboratory parameters observed in a patient with infectious hepatitis. Through most of the clinical course, SGP-T was less than SGO-T activity when hyperglobulinemia was present.

Acute homologous serum hepatitis, infectious hepatitis, and hepatitis associated with infectious mononucleosis, 32 during the initial or increasing icteric phase of the disease, are associated with SGO-T values up to 2,500 and SGP-T activity up to 3,600 spectrophotometric units. No difference has been observed between homologous serum and infectious hepatitis and the alterations of the serum enzymes. Although the changes in the activity of the two serum transaminases parallel each other, the rise of SGP-T usually exceeds that of SGO-T activity. However, when acute hepatitis is accompanied by hyperglobulinemia, due either to the severity of the hepatic infection or to antecedent underlying hepatic disease, SGO-T is greater than SGP-T activity, with both greater than 400 units during the increasing icteric phase (figures 8, 9).

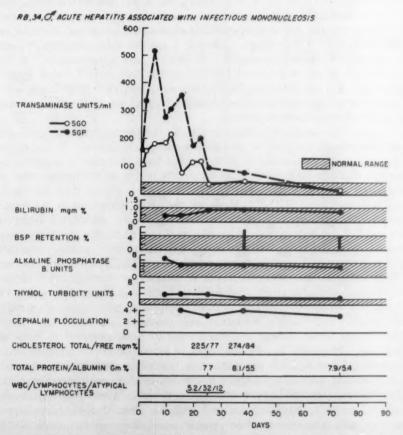


Fig. 10. Serial serum transaminase activities and other laboratory parameters observed in a patient with hepatitis associated with infectious mononucleosis. Throughout the clinical course, serum bilirubin was within the normal range.

Acute hepatitis without jaundice and/or without hyperbilirubinemia is associated with increased serum transaminase activities and with normal or slightly elevated SAL phosphatase activity. Figure 10 presents the laboratory data in a patient with acute nonicteric hepatitis associated with infectious mononucleosis; the serum total bilirubin remained within the normal range. In instances of nonicteric and subicteric hepatitis, alterations in SGP-T activity appear to reflect the presence and extent of hepatic inflammation. The subjective manifestations of nonicteric hepatitis appear to parallel alterations in SGP-T. In acute nonicteric or subicteric hepatitis, serum transaminase alterations facilitate detection of hepatic involvement and the study and control of viral hepatitis.

Hepatotoxic drugs produce hepatitis by a variety of pathophysiologic mechanisms, and upon the type of hepatic insult will depend the alterations in the serum enzymes. Carbon tetrachloride increases serum transaminase, and the levels attained depend upon the estimated amount and duration of toxic exposure. Other drugs, including azaserine, chlorpromazine, ³³ mercaptopurine, bishydroxycoumarin, salicylates ³⁴ and pyrazinamide, ²⁴ when hepatotoxic, result in increased SGP-T greater than SGO-T unless hyperglobulinemia from underlying hepatic disease is present. In all cases, with discontinuance of exposure to the hepatotoxic agent, the serum transaminase activities decrease toward normal.

Figure 11 summarizes diagrammatically the alterations in three serum enzymes as seen in a group of patients presenting with icterus. Extrahepatic biliary obstructive jaundice is differentiated from that due to hepatitis by the fact that the SAL phosphatase is usually higher in the former than in the latter. In both instances of jaundice, SGP-T is greater than the simultaneously measured SGO-T. However, the serial alterations in the serum enzymes in obstructive jaundice and that associated with acute hepatitis are readily distinguishable. Although toxic hepatitis due to drugs may mimic the serum enzyme alterations seen in obstructive jaundice, hepatitis due to toxic agents may be distinguished from acute hepatitis and obstructive jaundice; when the toxic insult is stopped by discontinuance of the hepatotoxic agent, the serum transaminases begin to fall toward normal, even though the serum bilirubin and/or SAL phosphatase may transiently remain unchanged. Intrahepatic carcinoma and lymphoma associated with jaundice present serum enzyme changes similar to those observed in cases of cirrhosis. However, in most instances of active Laennec's cirrhosis with hyperbilirubinemia, SAL phosphatase is normal or only slightly elevated, while in most cases of intrahepatic malignant neoplasia with jaundice, SAL phosphatase is elevated appreciably above normal. Postnecrotic cirrhosis, unlike Laennec's, may be associated with an elevated SAL phosphatase activity, and consequently may present serum enzyme alterations which mimic those observed in intrahepatic neoplasia with jaundice. Hemolytic jaundice in the adult is usually readily distinguishable from other causes of

jaundice; in most instances the serum enzymes remain normal except for transient and slight elevations in SGO-T, with no alterations of SGP-T above the normal range.

Cardiology: The impressive amounts of certain enzymes in cardiac musculature contrasted with the relatively small amounts of the respective enzyme activity in an equivalent amount of serum appear to result in significant elevations of serum enzyme activity in instances of myocardial damage presumably when the enzyme is released from necrotic cardiac tissue into the

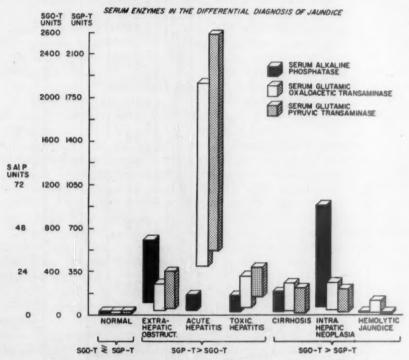
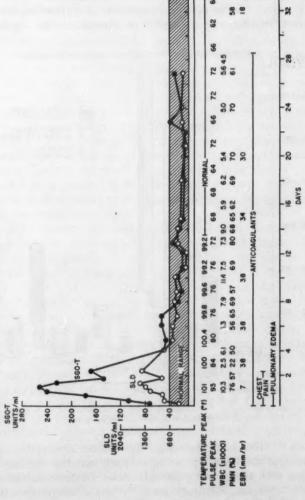


Fig. 11. Diagram of the range of change of three serum enzymes in a group of patients with jaundice due to various disease states.

blood stream.⁸⁵ This pathophysiologic mechanism appears to explain the observations that the following serum enzymes manifest increased activity in association with acute myocardial infarction: glutamic-oxaloacetic transaminase,^{18, 24, 36, 87} lactic dehydrogenase,^{88, 89, 40} malic dehydrogenase,²⁹ phosphohexoisomerase ²⁹ and aldolase.⁴¹

Transmural myocardial infarction in the human adult is associated with a rise in several serum enzyme activities which become manifest approximately six to 12 hours after the estimated time of coronary occlusion (figure

OR SO YR. OF ACUTE TRANSMURAL ANTERIOR MYOCARDIAL INFARCTION



Serial serum transaminase and lactic dehydrogenase activities and other laboratory and clinical parameters observed in a patient with acute myocardial infarction. FIG. 12.

12). The rise in serum enzyme activities reaches a peak within 24 to 48 hours, returning to the normal range by the fourth to the seventh day post-infarction. The peak enzyme activity elevations noted following myocardial infarction are two to 15 times normal. The peak rise and duration of abnormal serum enzyme activities appear to be proportional to the size of the infarction and/or the degree of myocardial necrosis. Following myocardial infarction, the rise in serum enzyme activity is not influenced by or correlated with blood pressure, heart failure, location of the infarction, digitalis or its derivatives, quinidine, age, sex, color, body temperature, sedimentation rate, leukocyte count or urinary output, or necessarily related to the configuration of the electrocardiogram. When the electrocardiogram is not diagnostic, or is obscured by changes of previous myocardial infarction, bundle-branch block, Wolff-Parkinson-White syndrome and other electrocardiographic aberrations, the rise in serum enzyme activity in a clinical setting suggestive of infarction is an especially helpful diagnostic parameter.

Changes in serum enzyme activity may contribute to delineating the process of myocardial necrosis in patients with substernal pain, not only in those suspected of having coronary occlusion but also in those with coronary insufficiency without occlusion. Serum enzyme activity remains within normal limits in patients with status anginosus or coronary insufficiency in spite of accompanying transient ST segment and T wave abnormalities. In clinical settings of acute coronary insufficiency when serum enzyme activities are elevated, the serum enzyme increments suggest that ischemia of cardiac muscle has been accompanied and/or followed by myocardial necrosis.

In most cases of pericarditis of various causes, pulmonary emboli with and without pulmonary infarction, ⁴³ cardiac arrhythmias and rheumatic carditis, no significant or consistent elevations in serum enzyme activity have been observed.

Oncology: Of the many body fluid enzymes studied in relationship to malignant neoplasia, those which have recently received clinical attention include lactic dehydrogenase, 44, 45, 46, 47, 48, 49 proteinase, 50, 51 phosphohexoisomerase, 52 glutathione reductase, 58 ribonuclease, 54 aldolase 55 and phosphoglucomutase. 56 None of the enzymes studied is completely reliable for the diagnostic appraisal of localized or disseminated neoplasia, and all of the body fluid enzymes are influenced by disease states other than malignant neoplasia.

Although histologic tissue examination remains the pivotal factor in the diagnosis of malignant neoplasia, there are diagnostic aspects in patients with neoplasia in which biochemical examination of body fluids may supplement and/or extend information derived from histologic study. Recent studies and observations suggest that the assay of serum lactic dehydrogenase (SLD) activity of body fluids, such as serum, serous effusion and cerebrospinal fluid (CSF), may contribute to the diagnosis of malignant neoplasia primarily in three clinical settings. In a patient with disseminated

cancer, lymphoma or myelogenous leukemia in whom the SLD is increased, the activity and/or rate of growth of the tumor may be roughly appraised by following the SLD; in such patients, response of the neoplasia to therapy may be reflected in return of SLD to normal. When malignant neoplasia involves the central nervous system (CNS), primary and metastatic tumors may not be reflected in abnormal cytologic flora of the CSF, and in these settings the measurement of CSF-LD may permit detection and/or con-

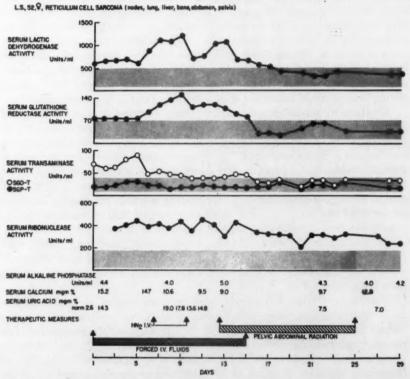


Fig. 13. Serial activities of six serum enzymes and other laboratory and clinical parameters observed in a patient who received treatment for reticulum cell sarcoma.

firmation of neoplastic involvement of the CNS. Finally, in the cytologic examination of serous effusions, the measurement of LD may serve to detect the presence of a serosal surface tumor which has failed to exfoliate cells into the effusion, or to exclude the presence of serosal surface neoplasia suspected because of the finding of atypical histiocytes and mesothelial cells in the serous fluid.

Many patients with myelogenous leukemia, lymphoma, sarcoma and disseminated carcinoma have increased SLD.^{44, 45, 47} The untreated or therapeutically resistant patient maintains elevated SLD or manifests increasing SLD with progression of the neoplastic disease. In those patients in whom neoplasia shows response to surgical, hormonal and/or ionizing radiation therapy, there is usually a decreasing activity of SLD, with return toward normal range as remission of the disease is attained. These serum enzyme changes are somewhat analogous to the alterations in serum acid phosphatase which accompany therapeutic responses in patients with metastatic

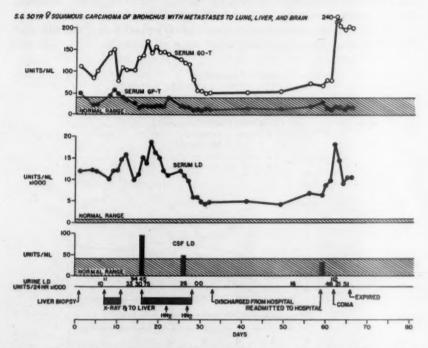


Fig. 14. Serial serum enzyme activities and other parameters observed in a patient with disseminated squamous carcinoma of the bronchus. The period of time between discharge from the hospital and re-admission to the hospital coincided with the clinical remission of the disease state, which was coincidentally related to diminution in serum and cerebrospinal fluid enzyme activities.

prostatic adenocarcinoma. However, the alterations of SLD associated with therapy in malignant neoplasia, unlike serum acid phosphatase in prostatic cancer, appear to be independent of the organ origin of the tumor and its disseminated distribution. Figure 13 depicts the serial changes in SLD and other serum enzyme and chemical parameters in one patient with widespread reticulum-cell sarcoma. Following treatment with nitrogen mustard and ionizing radiation, the tumor areas showed regression, the patient improved clinically, and coincidentally SLD as well as the other

studied parameters fell toward normal. Similar behavior of SLD has been observed following treatment in patients with disseminated carcinoma (figure 14), myelogenous leukemia and other malignant tumors. In some instances, SLD decrease may herald clinical remission following therapy, and, contrariwise, SLD may increase in the prodromal phase of relapse of the neoplastic disease process. The fall of SLD toward or to the normal range may occur following treatment in spite of the continued presence of tumor, and presumably the serum enzyme change is a reflection of the metabolic change in the tumor rather than of its presence in the body.

Other non-neoplastic disease states are associated with SLD increments.⁴⁴
These include acute myocardial infarction, acute hepatitis, both viral and

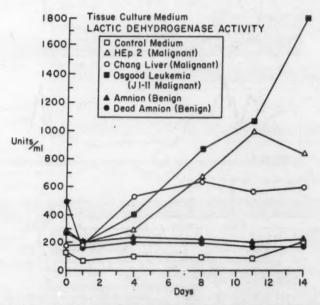


Fig. 15. Serial lactic dehydrogenase activity of medium contained in tissue cultures of various benign and malignant human cells.

homologous serum types, fulminant hemolytic episodes, dermatomyositis and muscle trauma. The serial SLD alterations usually seen in all but dermatomyositis are distinguishably dissimilar to those seen in untreated malignant neoplasia. Correlation of the clinical data with the SLD alterations usually permits delineation of the disease factors to which the SLD variations are attributable.

Serous effusions are derived from the plasma, and when pleural, pericardial and peritoneal serous effusion bathe or contain no malignant neoplastic tissue, the serous effusion has an LD activity less than the plasma (or serum) from which it is derived. In patients with infectious and degenerative disease states, LD activity of the effusion is less than that of the serum. In patients with localized and disseminated malignant neoplasia associated with serous effusions which do not bathe and do not contain malignant cells, LD activity of the serous effusion is less than the SLD of the respective patient. In patients with malignant neoplasia with serous effusions which contain malignant cells on cytologic and/or histologic examination, LD activity of the effusion is greater than the respective SLD.⁵⁷ No relationship has been found between effusion LD activity and the volume, color, specific gravity, total protein content, erythrocyte and leukocyte constituents of the effusion. In some patients with serous effusions in association with neoplasia, cytologic examination of the effusions reveals no malignant cells, although the effusion LD activity is greater than that of

TABLE 3

The Lactic Dehydrogenase Activity of Serum and Peritoneal Fluid and the Results of Cytologic Study of the Peritoneal Effusion Obtained from a Patient with Adenocarcinoma Metastatic to the Peritoneal Surface

In each instance, the peritoneal fluid lactic dehydrogenase activity is greater than the lactic dehydrogenase activity of the respective serum.

S. M., 77 yrs., uterine adenocarcinoma (Grade 3), peritoneal metastases with ascites

Hospital Day		ectivity per ml.	Peritoneal Fluid Cytologic Exam ination for Malignant Cells
Zay	Serum	Effusion	(Smear and Cell Block)
6 7	800 1,000	1,200 1,300	Negative Positive*
11 12	2,000	4,700 radioactive gold)	
18 25 31	1,700 2,400 Died	3,300 3,000	Positive (class V) Positive (class V)

^{*} Sp. gr. 1.015; protein 3.7 gm. %.

the respective SLD. In most of those instances, malignant tumor has been found on the serosal surface which was bathed by the respective effusion. It would appear that effusion LD greater than the respective SLD activity is found in clinical settings in which the serous effusion contains and/or bathes proliferating malignant cells.

Some patients with ovarian and breast carcinoma have effusions which contain malignant cells but have effusion LD activity less than SLD activity. In each instance observed the patient was receiving hormonal, steroid or other treatment which appeared to influence the neoplasia. It appears that a therapeutic modality may have influenced LD contribution and other metabolic aspects of the malignant cells in the serous effusion without eradicating the neoplastic cells from the effusion.

The mechanisms by which the LD activity of serous effusion containing

or bathing malignant cells is increased beyond the activity of the serum from which it is derived are presumably related to the contribution to the effusion of LD by the proliferating malignant cells ⁵⁸ (figure 15). Lactic dehydrogenase is a globulin, and studies have suggested that, although the water of an effusion exchanges with that of the vascular compartment, globulins within an effusion do not exchange so readily; if continuously added, LD globulin accumulates in the effusion. ⁵⁹ Any therapeutic agent influencing malignant cellular proliferation and/or metabolism will affect the LD contribution of the cellular flora of an effusion.

Effusions which are purulent, chylous or hemolyzed do not lend themselves to LD study as a parameter of malignant cytologic constituency. Necrotic and/or destroyed leukocytes and erythrocytes contribute LD to effusions without regard to neoplastic character.

TABLE 4

The Lactic Dehydrogenase Activity of Serum and Pleural Fluid and the Results of Cytologic Study of the Pleural Effusion Obtained from a Patient with Reticulum Cell Sarcoma Implanted on the Pleural Surface

Although the cytologic observations are inconclusive, effusion lactic dehydrogenase is greater than is serum LD activity. Postmortem examination revealed reticulum cell sarcoma implants on the right pleural surface.

V. M., 50 yrs., 9, reticulum cell sarcoma

Hospital Day	Righ	t Pleural Eff	fusion	Dehyd	rogenase s/ml.	aral Effusion	
	Amount	Color	Protein	Serum	Effusion	Smear .	Cell Block
1	2,000	Bloody	2.9	780	1,900		pical nuclei. May be a small cell tumor to be ruled out
12	1,200	Amber	2.3	760	1,700 .	Poorly preserved atypical cells present	Few abnormal present

The use of LD activity to characterize the malignant cellular constituents of a serous effusion appears to offer promise of complementing the conventional cytologic technics. Tables 3, 4 and 5 present data which demonstrate clinical instances in which measurement of LD activity of serous effusions proved helpful clinically and supplemented information obtained from cytologic examination of the respective effusions.

Neurology: The blood-brain barriers serve to make the changes in the cytologic and noncellular constituents of the CSF relatively independent of the alterations in the vascular fluid compartment. Accordingly, it has been observed that CSF enzyme changes are for the most part uninfluenced by serum enzyme alterations, and vice versa. Among the CSF enzymes recently stadied in relation to CNS disease are glutamic-oxaloacetic trans-

aminase, 60, 61, 62, 63 ribonuclease, 67 lactic dehydrogenase 64, 65, 66 and glutathione reductase. 53 Experience with the clinical use of the CSF enzymes is limited, and further studies in this clinical area will be required to define clearly the reliability of these technics.

Glutamic-oxaloacetic transaminase alterations of CSF have been observed in association with cerebral infarction secondary to cerebrovascular hemorrhage, thrombosis and embolism. However, the inconsistency of the enzyme changes suggests that transaminase alterations of CSF are unreliable in the diagnosis of CNS disease.

Malignant neoplasia of the CNS is associated with increased CSF-LD activity which is not proportional to the physical, chemical or cellular parameters of the CSF and is independent of SLD. Presumably, the increased CSF-LD results in part from the contribution of LD by the proliferating

TABLE 5

The Lactic Dehydrogenase Activity of Serum and Peritoneal Fluid and the Results of Cytologic Study of the Peritoneal Effusion Obtained from a Patient with Wilms's Tumor of the Left Kidney

Although no malignant cells were found on cytologic examination of the serous fluid, effusion lactic dehydrogenase is greater than is the enzyme activity of the respective serum. Postmortem examination revealed metastatic deposits on the peritoneal surface, although apparently the malignant cells did not exfoliate in numbers great enough to be detected cytologically.

S. P., 7, male, Wilms's tumor, left kidney; metastases to peritoneal surface of diaphragm, parietal pleura, heart and lungs (postmortem 5/23/57)

		Ass	cites		Serum LD	Effusion LI
	Volume (ml.)	Color	Protein (gm. %)	Cytology	(unit	s/ml.)
4/11/57 5/20/57	2,700 3,200	Sang. Sang.	3.9 3.7	Neg. Neg.	1,600 2,200	2,000 3,400

malignant cells. The increased CSF-LD persists or increases further unless surgical, chemical or radiation therapy influences the CNS neoplastic lesion. Patients with malignant neoplasias which do not involve the CNS, and patients with disease states without CNS involvement, have normal CSF-LD activity of 40 or less units per milliliter, regardless of the respective SLD.

In addition to malignant neoplasia of the CNS, other CNS diseases are associated with increased CSF-LD activity; this group consists of bacterial and viral meningitis, subarachnoid hemorrhage and cerebrovascular accidents, including thrombosis, hemorrhage and embolism. The clinical setting, along with the serial alterations in CSF-LD activity, usually permit diagnostic differentiation from CNS neoplasia. Although not all patients with cerebrovascular accidents show increased CSF-LD, in those instances where it occurs there is a gradual decrease in CSF-LD activity unlike that observed in untreated CNS neoplasia (figure 16). The elevated CSF-LD

activities associated with meningitis fall rapidly toward normal with treatment of the meningeal infection (figure 17). Most other CNS diseases studied are associated with CSF-LD activity within the normal range.

Several instances of CNS neoplasia associated with normal CSF-LD activity have been observed. It appears that if a tumor is located extradurally, no increased CSF-LD is found. In addition, if a CNS tumor is situated so as to distort the anatomic relationships of the ventricular system, thereby preventing the CSF bathing the tumor area to drain into the main stream of CSF, no increase in spinal fluid LD activity may result; such phenomena have been observed in the presence of primary brain tumors.

Spinal fluid made sanguineous as a result of trauma from tapping the

8,52, M.B., CEREBRAL EMBOLUS (1/21/58)

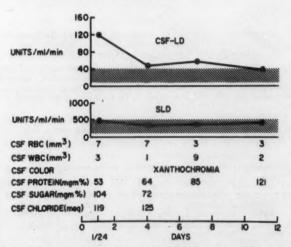


Fig. 16. Serial cerebrospinal fluid lactic dehydrogenase activity and other laboratory parameters observed in a patient with a cerebral infarct.

fluid cannot be used for the measurement of CSF-LD. The enzyme findings of such fluids are misleading because the CSF is contaminated with plasma which normally contains four or more times the LD activity of CSF.

Other Specialties of Medicine: Various forms of primary muscular and neuromuscular diseases are associated with elevated serum enzymes, including cholinesterase, ⁶⁸ glutamic-oxaloacetic ^{69, 70} transaminase ^{71, 72, 73, 74} and aldolase. ^{75, 76, 77} Increased SGO-T and aldolase have been observed in muscular dystrophy, including pseudohypertrophic muscular dystrophy, dermatomyositis and paroxysmal myoglobinuria. In the case of dermatomyositis, abnormally high values are found in patients during the acute phase of the disease, and serial determinations show a parallelism between decreasing

values of SGO-T activity and clinical improvement. Serum transaminase determinations appear to constitute a useful index of the clinical activity of dermatomyositis. Most of the other neuromuscular diseases studied have been associated with normal transaminase activity.

Blood enzymes play a role in the blood clotting phenomenon, although there does not appear to be complete agreement as to which of the multi-

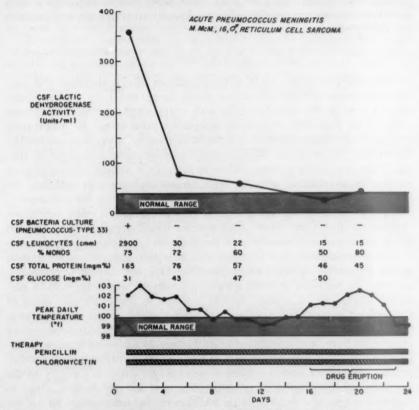


Fig. 17. Serial cerebrospinal fluid lactic dehydrogenase activity and other laboratory, clinical and therapeutic factors observed in a patient treated for pneumococcus meningitis.

plicity of factors concerned are enzymes.⁵ The conversion of prothrombin to thrombin is said to result from the activity of prothrombinase. Increasing attention has been given to fibrinolysin, an enzyme which appears to influence blood clotting adversely in certain clinical settings.^{78, 79, 80, 81, 82} Fibrinolysin exists in the blood in its inactive form, plasminogen, and is activated to its proteolytic form under certain conditions. Following thoracic surgery, increased fibrinolysin has been observed and may account for

postoperative oozing and hemorrhage. This phenomenon presumably results from the release of plasminogen activator from the lungs during surgery, resulting in increased conversion of plasminogen to plasmin and causing increased fibrinolysis. Increased fibrinolysis has been observed in patients with leukemia. Following hepatic lobectomy, an excessive degree of oozing was found to be related to the fibrinolytic activity of the blood.

Although serum blood enzymes have been studied in patients with psychiatric disease, no definitive diagnostic correlation appears to have been derived.^{85, 84, 85}

CONCLUSIONS

The ever-increasing use in clinical medicine of the abundant and continuously accumulating information about tissue and body fluid enzymes appears to be providing the clinician with a larger aggregation of laboratory tools. Like that derived from all laboratory parameters, the information derived from measurement of body fluid enzyme activities has noteworthy limitations. Most if not all enzymatic reflections are nonspecific in that more than one etiologic factor and more than one anatomic site can account for similar quantitative and/or serial enzyme changes. In addition, the multiplicity of enzymes present in body fluids, as well as the influence of other body fluid constituents, such as inhibitors, antienzymes, activators, competitors, drugs and others, may account for apparent artefacts included in the extensive enzyme activity of the body fluid. However, the concomitant measurement of several enzymatic activities and clinical correlation makes it possible at times to pinpoint the type and site of a pathologic process. In addition, in some instances, serum enzyme changes have permitted recognition of disease such as hepatitis in the prodromal phase of the malady; in other instances, such as drug toxicity, serum enzyme alterations have indicated pathologic effects at a time when other laboratory parameters have been uninfluenced; in the case of suspected myocardial infarction associated with bundle branch block or other masking electrocardiographic aberrations, serum enzyme changes may contribute pivotally to the resolution of the diagnostic problem. The use of body fluid enzymes to supplement cytologic technics is an addition to the armamentarium for the study of patients with oncologic diseases. As the mechanisms, significance and limitations of tissue and body fluid enzymes are better understood, more extensive application of enzymatic technics to clinical medicine will ensue.

SUMMARIO IN INTERLINGUA

Processos pathologic in le histos, de character inflammatori, neoplastic, o degeneratori, pote resultar in marcate alterationes enzymatic que alora es reflectite in comparabile systemas de enzyma in le sanguine e in altere liquidos del corpore. A parte le exploitation diagnostic de studios del enzymas seral del typo de phosphatase alcalin e acide, prothrombina, amylase, e lipase, alterationes observate in varie altere enzymas ha essite utilisate pro objectivos diagnostic in multo diverse campos del medicina interne. Il ha essite monstrate que acute infarcimento myocardial es associate con augmentos del nivellos seral de transaminase glutamic-oxaloacetic, dishydrogenase lactic, dishydrogenase malic, e aldolase. In le campo de gastroenterologia, attention ha essite prestate particularmente al observation de alterationes in le nivellos seral de transaminase glutamic-oyaloacetic como addition al methodos del diagnose differential de jalnessa. Le medicina oncologic utilisa pro objectivos diagnostic le observation que histos maligne in stato de crescentia rapide contribue dishydrogenase lactic al liquidos que bania cellulas neoplastic.

Le correlation de alterationes del activitate de varie enzymas in le liquidos del corpore con varie situationes clinic deveni de plus in plus importante in le medicina interne. Es presentate un revista del disveloppamentos recente in le campo del enzymatologia clinic. Seligite exemplos es presentate e discutite ab le puncto de vista del utilitate de iste methodos pro le objectivos del medicina clinic.

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SICKLE CELL-HEMOGLOBIN D DISEASE *

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Soon after the discovery that sickle (S) hemoglobin can be differentiated from normal (A) hemoglobin by electrophoresis, to ther abnormalities of hemoglobin were recognized. In studying a white patient who previously had been thought to have sickle cell anemia, Itano 2 found that the erythrocytes of the mother could not be made to sickle, although the electrophoretic pattern was indistinguishable from that of sickle cell trait. The abnormal hemoglobin which did not produce sickling also differed from S hemoglobin because of its normal solubility in the reduced state, and was subsequently designated as hemoglobin D. The atypical hemolytic disorder in the patient had resulted from the inheritance of hemoglobin D from the mother and hemoglobin S from the father, and was identified as sickle cell-hemoglobin D (S-D) disease.

Hemoglobin D has been encountered in other individuals, most of whom were apparently heterozygous for both hemoglobins A and D (D trait). In contrast to the preponderant occurrence of hemoglobins S and C among Negroes, most instances of hemoglobin D were discovered among non-Negroes. An abnormality identified as D trait was encountered in two Algerian Musselman families,8 a Turkish family 4 and in several Sikhs.8 In a survey in India, Bird and his associates 6 found hemoglobin D in five of 274 Sikhs and in one of 13 Punjabi Hindus. Chernoff reported that hemoglobin D was present in four of 1,000 Negroes examined in St. Louis.7 In a survey of 1,000 Negroes in Baltimore, one instance of hemoglobin D trait was recognized.8

Hynes and Lehmann 9 encountered a patient with a disorder which was presumed to be D-thalassemia. An asymptomatic Sikh soldier was demonstrated to have only hemoglobin D and was considered to have homozygous hemoglobin D disease.10 A case of S-D disease was described by Dacie 11 and another by Stewart and MacIver. 12 Further details of the original S-D family were reported by Sturgeon, Itano and Bergren. 18 In all of these cases hemoglobin D was inherited from non-Negroes, most of whom were said to be English. In addition, Chernoff observed an instance of homozygous hemoglobin D disease in a Negro.

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Following the recognition of S-D disease in a Caucasian boy who attended the clinics of The Johns Hopkins Hospital, a study of a large number of his relatives on both the material and the paternal sides of the family was performed. The interesting features of the S-D disease and some genetic observations are reported here.

CASE REPORT

This patient was first admitted to the Harriet Lane Home of The Johns Hopkins Hospital in 1943. His birth and development had been normal. When 14 months old he began to experience recurrent pain and swelling of the hands and feet. Attacks occurred at intervals of two to three months and often persisted for several days. At age three there were episodes of abdominal pain associated with nausea and vomiting and rigidity of the abdominal wall. Pallor and jaundice were noted between and during attacks of pain. At age five he began to experience pain in the arms and legs, sometimes requiring narcotics for relief. Diagnoses of infectious arthritis and of congenital hemolytic jaundice had been considered. Because of the persistence of the symptoms he was referred to The Johns Hopkins Hospital.

At the time of his first admission, at age six, the patient was pale and jaundiced. Transient soft tissue swellings and tenderness were noted over the dorsal surfaces of both feet. The heart was slightly enlarged to the left and to the right. The liver and the spleen were palpable. The child was examined by Dr. Harriet Guild, who was impressed that the clinical manifestations resembled those of sickle cell anemia. Sickling of the red cells was demonstrated in a preparation of fresh blood. The patient returned to his home and was not seen again at The Johns Hopkins Hospital

until 1956

Attacks of pain in the abdomen and in the extremities became less frequent, and at times there were asymptomatic intervals of months, and on one occasion of two years. At age seven, large ulcers appeared on the lower legs and healed after several weeks. During adolescence the patient developed episodes of dull aching pain in the lower back, at times so severe that large doses of morphine were required for relief. In the interval between episodes he was remarkably well, participated in vigorous athletics and was champion water skier in his district. He was chronically anemic. His physician reported that the hemoglobin was usually between 60 and 80%, although on occasions it was 45%. At times the patient was given multiple transfusions of whole blood, generally with the result that the hemoglobin level was not substantially increased. The urine was said to have been dark on many occasions, and was extremely dark during bouts of severe pain. As a child, the patient had repeatedly had bronchitis, with occasional episodes of pneumonia. At about age 17 he began to have frequent attacks of chest pain associated with cough, dyspnea and cyanosis, invariably following the onset of pain in the low back region. On many of these occasions, x-rays showed consolidation of one lobe or another of the lungs. At age 18 he was hospitalized several times because of pneumonia.

The patient returned to The Johns Hopkins Hospital in 1956 at age 20. At the time of examination he was asymptomatic. He was well developed, well nourished, short and muscular. He did not appear acutely or chronically ill. He had blond hair, a very fair complexion and blue eyes. The axillary and pubic hair was normal. The fingers were short and stubby. The symphysis-to-sole measurement was 10 cm. longer than the crown-to-symphysis measurement; however, the appearance was not that of long extremities, but rather of a shortened trunk (figure 1). There was moderate pallor of the nail-beds and of the conjunctivae, and the sclerae were slightly jaundiced. The optic fundi revealed a marked degree of tortuosity of the retinal

vessels. The heart was enlarged to the left and slightly to the right. The sounds were of good quality, and no murmur was heard. The lungs were clear. The spleen could not be palpated. The genitalia were fully developed. No tenderness or discernible abnormality was found in the sacral region, where he had experienced the many episodes of pain. The hematocrit value was 30%; hemoglobin, 9.6 gm. per 100 ml. of blood. The red cell indices included an MCV of 105 cubic microns, an

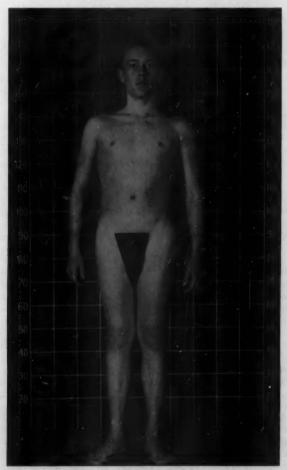


Fig. 1. Patient with sickle cell-hemoglobin D disease at age 19. Scale is in centimeters.

MCH of 34 micromicrograms and an MCHC of 31%. The white cell count was 20,300 per mm³, with 12% juvenile forms, 59% polymorphonuclear leukocytes, 16% lymphocytes, 10% monocytes and 3% atypical lymphocytes. There were 510,000 platelets per mm³, and the reticulocyte c.unt was 13.3%. Examination of the fixed blood smear revealed pronou.ced anisocytosis, with a large number of target cells and a few sickle cells (figure 2). Sickling of the red cells occurred promptly with

sodium metabisulfite. The serum bilirubin was 2 mg. per 100 ml., of which 1.1 mg. were direct reacting. The electrocardiogram was normal. A roentgenogram of the chest revealed clear lungs and a moderately enlarged heart. There was severe demineralization of the skull and of the thoracic and lumbar spine, with indentation of the superior and inferior articular surfaces of the vertebral bodies, thought to be secondary to the osteoporosis. In the long bones there was a slight lack of moulding, with transverse lines running through the spongiosa and the shafts of the femur, tibia and radius. The trabecular pattern of the long bones and pelvis was not significantly abnormal. A roentgenogram of the chest which had been exposed during a previous episode of severe back pain, dyspnea and cyanosis revealed extensive consolidation of the lower part of the right lung. Smaller areas of infil-

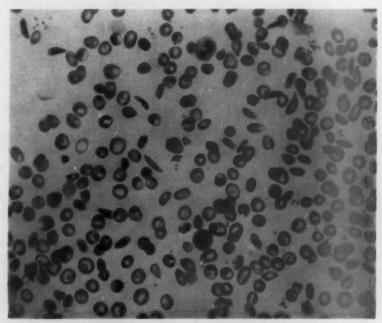


Fig. 2. Blood smear of patient with sickle cell-hemoglobin D disease.

trate were seen in the left midlung. A film made one week later showed complete clearing of these consolidations. The osmotic fragility of erythrocytes before and after incubation was measured. There was increased resistance with less than 50% hemolysis in 0.25% saline, and only 80% hemolysis in 0.2% saline (figure 3). Incubation for 24 hours resulted in an increase in fragility toward the normal range, although some of the cells remained resistant. The mechanical fragility was 9% before incubation, and increased to 27% after incubation. Electrophoresis of the hemoglobin on filter paper at pH 8.6 revealed one spot with the mobility of S hemoglobin.

The patient returned for reëvaluation one year later. During the summer he had experienced very little difficulty, but during the winter episodes of severe pain in the arms and legs had required hospitalization and the administration of narcotics.

He had had one episode of pneumonia for which he was also hospitalized. On examination, the striking appearance of good health and muscularity was again noted. The results of examination of the blood were similar to those previously recorded.

The patient was last seen at age 21 in 1957. Because of the regularity with which the episodes of pain occurred during the night, he was advised to take 10 gm. of sodium bicarbonate at bedtime. During this therapy, he continued to experience nocturnal episodes of severe pain in the back and the extremities.

FRAGILITY OF ERYTHROCYTES IN HB D DISORDERS

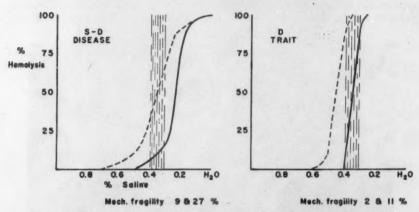


Fig. 3. Osmotic fragility of the erythrocytes of the patient (left) and of his mother (right). Solid line: fresh red cells. Dotted line: after incubation of blood at 37° C. for 24 hours. Shaded area: normal range of fragility for unincubated cells. The mechanical fragility before and after incubation is recorded as per cent hemolysis.

In summary, this patient was a young white man with fair skin, blue eyes, blond hair and sthenic habitus, with no features suggestive of negroid ancestry. He had had recurrent episodes of severe pain in the back and extremities dating from early infancy, and many episodes of "pneumonia," transient ulcers of the lower legs and a chronic hemolytic anemia. Nevertheless, he maintained the general appearance of good health and was an accomplished athlete. Although his red cells had been demonstrated to sickle and the electrophoretic pattern of the hemoglobin was that of sickle cell anemia, a diagnosis of homozygous sickle cell disease was questioned because of the many atypical features. Accordingly, additional studies were performed, on the basis of which it was apparent that the patient had S-D disease rather than sickle cell anemia.

The mother of the patient had very fair skin, graying brown hair and blue eyes. There were no negroid features. Electrophoresis of her hemoglobin on filter paper at pH 8.6 revealed a pattern indistinguishable from that of sickle cell trait. The red cells failed to sickle on repeated attempts using various reducing agents. The hematocrit value was 44% and the erythrocyte indices were normal. There were 2.5% reticulocytes. Serum

bilirubin value was normal. The electrophoretic pattern, together with the absence of sickling, established the diagnosis of hemoglobin D trait.

The father was very short and stocky in appearance, with a round face, large chest and short stubby fingers reminiscent of those of the patient. He had a fair complexion, graying hair and blue eyes. There were no negroid features. Electrophoresis of the hemoglobin of the father showed a pattern of sickle cell trait, and sickling of the erythrocytes was promptly induced with sodium metabisulfite. The hematocrit value and the red cell indices were normal. A few target cells were noted on the fixed blood smears.

KINDRED WITH S & D HEMOGLOBINS

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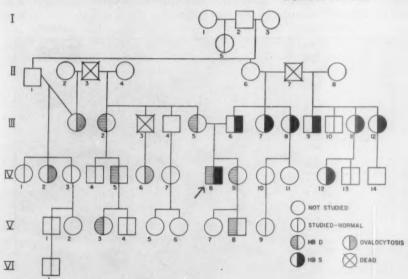


Fig. 4. Kindred with S and D hemoglobins.

A field trip was made to several North Carolina coastal communities in which relatives of the patient dwell. This family had resided in North Carolina for several generations, and ancestors of both parents of the patient had come from England. Eleven relatives of the father were available for study (figure 4). All were apparently in good health, and none had any negroid features. Electrophoresis of the hemoglobin showed that seven members, including the father, had sickle cell trait, and red cells from all of these could be made to sickle. A portrait of the paternal grandfather of the patient showed a striking resemblance to the patient.

Fifteen relatives of the mother were available for study. In six of these, including the mother, the electrophoretic pattern was indistinguishable from that of sickle cell trait, but in none could the erythrocytes be made to sickle. Examination of blood smears of these individuals revealed no abnormalities, and they were considered to have hemoglobin D trait. In three members of this family, in whom the electrophoretic pattern showed only A hemoglobin, the blood smears revealed ovalocytosis. All of these individuals appeared to be well.

Robinson and his associates ¹⁴ have demonstrated that hemoglobins S and D can be separated by electrophoresis on agar plates at pH 6.2. Their method was employed to study the hemoglobin of the patient. The electrophoretic pattern on agar (figure 5) shows two major components with the mobilities of hemoglobins S and D. In addition, a smaller component with the mobility of fetal hemoglobin is present.

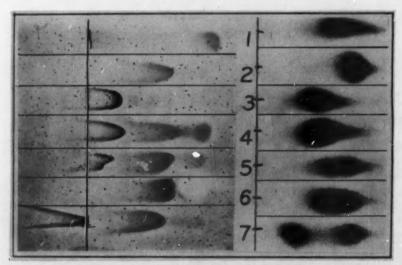


Fig. 5. Electrophoretic pattern of hemoglobin on agar at pH 6.2 (left) and on filter paper at pH 8.6 (right). Blood specimen was obtained from (1) normal umbilical cord (hemoglobin F); (2) normal adult (hemoglobin A); (3) patient with sickle cell anemia (hemoglobin S); (4) the patient with sickle cell-hemoglobin D disease (hemoglobins S-D-F); (5) person with sickle cell trait (hemoglobins S-A); (6) person with hemoglobin D trait (hemoglobins A-D); (7) person with hemoglobin C trait (hemoglobins C-A).

Discussion

The worldwide distribution of hemoglobin D has not been determined. Limited studies have revealed a high gene frequency for this abnormality in India among Sikhs and Punjabi Hindus, and its occurrence has been noted among other non-Negroes, particularly those of English origin. In the United States hemoglobin D was found among Negroes with an incidence

of 0.1 to 0.4%. The occurrence of hemoglobin D among Caucasians in the United States must be rare, since no hemoglobin D was encountered among 500 randomly selected white individuals in Baltimore ¹⁵ and among 350 white individuals in Houston. ¹⁶ Sickle cell-hemoglobin D disease, however, has been recognized only in Caucasians (table 1). It is possible that instances of S-D disease have been overlooked in Negroes because of the similarity of S-D disease to homozygous sickle cell anemia (S-S). Silver, Simon and Clement encountered a Negro child who was first thought to have hemoglobin C-D disease ¹⁷ but subsequently was found to have sickle cell-hemoglobin C disease. ¹⁸

An electrophoretic pattern of hemoglobin on filter paper which shows only one concentration peak with the mobility of S-hemoglobin does not allow a diagnosis of homozygous sickle cell anemia, since an identical pattern may be seen in sickle cell-thalassemia (S-thalassemia)19 and S-D disease.2 When such a pattern is encountered in a white individual, the likelihood that the disorder is S-thalassemia or S-D is much greater than that sickle cell anemia is present. Other features of the entire clinical picture are of considerable importance in making positive differentiations. With few exceptions, sickle cell anemia is a hemolytic disorder of unremitting severity, characterized by marked anemia and constant jaundice, severe episodes of pain and a typical habitus. While individuals with S-thalassemia or S-D disease may experience an early and severe onset of recurrent episodes of pain and may exhibit a degree of anemia which is quite as severe as that of sickle cell anemia, there are usually atypical clinical features. Individuals with S-thalassemia or S-D disease are usually of normal habitus, frequently experience long periods of clinical remission, and may at times be found to have only mild anemia, or to be nonanemic. In the study of the patient whose clinical manifestations are reported here, the severity of the episodes of pain in the lower back and extremities, recurrence of hemolytic episodes and the recurrent episodes of pneumonia, together with the finding of numerous sickle cells on the fresh blood smears, suggested a diagnosis of sickle cell anemia, although the fact that he was white with no negroid features, had a normal habitus and at times had only mild anemia suggested strongly that this was a genetic variant of sicklemia. Itano 2 has demonstrated that the solubility of reduced D hemoglobin is normal, while that of reduced sickle hemoglobin is markedly decreased. Thus, determination of the hemoglobin solubility will serve as a differentiating point between S trait (S-A) and D trait (D-A), or between sickle cell anemia (S-S) and S-D disease. Attempts were made in the present case to establish a diagnosis of S-D disease on the basis of the solubility of reduced hemoglobin, but while the results were suggestive, they were not conclusive. On the other hand, electrophoresis of the hemoglobin on agar at pH 6.2 resulted in a pattern quite unlike that of sickle cell anemia and provided impressive

Case	Authore	Age	Disenseis	Ancestry	stry	Clinical	Hemato-	Characteristics of	Reticu-	Bilirubin	Fragility of
	ammu	Sex	Ling Hosis	Mother	Father	Manifestations	15%	Erythrocytes	%	mg./100 ml.	Erythrocytes
	Sturgeon, Itano and Bergren ¹⁸	M M	S-D disease	Irish, English, American- Indian	Irish, English (Positive sickling)	Repeated severe bone and joint pains. Moderate anemia	30	MCV 113 MCHC 30 Sickled cells, rare target cell	∞	1.2	Normal
	Sturgeon, Itano and Bergren ¹³	23 F sister of No. 1	S-D disease	(D trait)		Occasional mild joint pain. Moderate anemia	33		-	9.0	Normal
	Dacie ¹¹	9 H	S-D disease	Spanish, Austrian (D-trait)	Jamaican, Irish, French (S-trait)	Chronic infec- tions, moderate anemia, splenomegaly	27 (est.)	Polychromato- philia, hypo- chromia, some target cells	6	2.1	Osmotic decreased, mechanical increased
	Stewart and MacIver ¹⁸	31 F	S-D disease	English (D-trait)	African	"Symptoms of sickle cell anemia." Died, had scarred spleen	26 (est.)				
	Hynes and Lehmann	∞r-	D-thal, disease	Persian	Persian (? thal.)	Vague pains, mild anemia	35	MCV 65 MCH 21 MCHC 32 Anisocytosis,		8.0	Osmotic
	Bird and Lehmann ¹⁰	25 M	D.D disease	Sikh	Sikh	Well	45	MCV 63 MCH 18 MCHC 28		0.3	Decreased
	Smith and Conley	20 M	S-D disease	English (D-trait)	English (S-trait)	Severe bouts of bone, joint, abdominal pain. Pneumonia, chronic anemia	30	MCV 105 MCH 34 MCHC 31 Sickled cells, target cells, poly- chromatophilia, stippling, nu- cleated RBD.	13	2.7	Osmotic decreased, mechanica increased

confirmation of the diagnosis. In addition to S and D hemoglobins a smaller amount of fetal hemoglobin appears to have been present.

A diagnosis of S-D disease was made in our patient when the electrophoretic pattern of the mother suggested S trait, and sickling of the erythrocytes could not be produced. Investigation of the family of the mother revealed five other individuals with hemoglobin D trait. From figure 4 it is apparent that the inheritance of hemoglobin D could be explained by an autosomal mendelian dominant character, a mode of inheritance which has been suggested by previous genetic data. Hemoglobin S was encountered in the father of the patient and in six other members of his family. Since the patient's paternal grandfather married twice and S hemoglobin appeared in children of each marriage, it is almost certain that he carried the S gene. A portrait of this individual bears a striking resemblance to the patient and is dominated by blond hair, blue eyes and clear complexion. He is said to have come to America from England, and no negro ancestry is suspected.

Constituting an incidental finding in the family study was the presence of ovalocytosis on blood smears of four members of the mother's family. The distribution of ovalocytosis in the kindred established that the inheritance was from a male in the second generation (II-3 on figure 4), who may

have contributed the D gene as well.

Although it was possible to establish a diagnosis of S-D disease in this patient, the pathogenesis of many of the curious manifestations of the disease remains a puzzle. It is striking that the episodes of severe pain in the extremities or back almost always began at night. Typically, exposure to cold in the afternoon seemed a predisposing factor, and the time of onset was usually about 3:00 a.m. It might be speculated that stagnation and local de-oxygenation of the blood during sleep accentuated the tendency of the erythrocytes to sickle. Pulmonary manifestations in this patient always occurred in conjunction with the episodes of bone pain, suggesting that the pulmonary lesions were attributable to the sickling disorder, possibly because of occlusion of vessels in the pulmonary vascular tree by sickled erythrocytes. An alternative theory is that the episodes of bone pain were associated with infarcts of the bone marrow and the release of fat emboli to the pulmonary tree. Multiple bone marrow and fat emboli have been encountered in several instances of fatal sickle cell anemia and in one case of S-C disease where acute pulmonary manifestations were associated with bone pain.20 Clear evidence has been gained in studies of other forms of sickle disease to show that the train of pathologic events which begins with in vivo erythrocyte sickling and leads to obstruction of vasculature is more easily set off in the presence of progressively larger amounts of sickle hemoglobin. Our patient had substantially less S hemoglobin in his erythrocytes than does an individual with sickle cell anemia. Yet the episodes of bone and joint pain were as severe in this individual as in the majority of persons with sickle cell anemia.

This patient with S-D disease had a chronic hemolytic disorder which on occasions was markedly accentuated. On many occasions during his younger years he was given blood transfusions, but there is little indication that they were ever needed to relieve symptoms. On the contrary, the recurring disability was chiefly attributable to episodes of severe pain. In some patients with genetic variants of sickle cell disease, incapacitating and even fatal manifestations have occurred in the absence of an appreciable degree of anemia.

Since it is clear that sickle cell disease in the form of S-thalassemia or S-D disease may occur in white individuals, this disorder must be considered in the differential diagnosis of clinical manifestations which resemble those associated with sickle cell anemia, even when anemia is not severe.

SUMMARY

A Caucasian male from North Carolina was proved to have sickle cell-hemoglobin D disease. His clinical course was characterized by anemia, recurrent jaundice, pain in the extremities and back, and repeated episodes of pneumonitis. Sickling of his erythrocytes could be produced and the electrophoretic pattern of his hemoglobin on filter paper at pH 8.6 could not be distinguished from that of sickle cell anemia. On agar plates at pH 6.2, however, there was clear separation of the S and D components, and a smaller component with the mobility of fetal hemoglobin was also demonstrated. The mother of the patient and five of her relatives were found to have hemoglobin D trait. The patient's father and six of his relatives had the sickle cell trait. In neither lineage was there evidence of Negro ancestry. The genetic data which were obtained support the belief that hemoglobin D is an allele of the A, C and S hemoglobins.

SUMMARIO IN INTERLINGUA

Le presentia de morbo a cellulas falciforme e hemoglobina D esseva demonstrate in un masculo de racia blanc in Nord-Carolina. Su curso clinic esseva characterisate per anemia, recurrentia de jalnessa, dolores in le extremitates e in le dorso, e repetite episodios de pneumoritis. Falciformation de su erythrocytos poteva esser evocate, e le patrono electrophoretic de su hemoglobina in papiro-filtro a pH 8,6 non esseva distinguibile ab illo de anemia a cellulas falciforme. Tamen, in plattas de agar a pH 6,2, il occurreva un clar separation del componentes S e D, e un plus micre componente con le mobilitate de hemoglobina fetal esseva etiam demonstrate. Esseva constatate que le matre del patiente e cinque de su consanguineos habeva le tracto de cellulas falciforme. Nulle evidentia de ancestria negre existeva in le lineage materne o in le lineage paterne. Le datos genetic que esseva obtenite supporta le opinion que hemoglobina D es un allel del hemoglobinas A, C, e S.

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SALT METABOLISM IN HYPERTENSION * †

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It is an established fact that sodium chloride metabolism is abnormal in essential hypertension. However, the exact role which the disordered salt metabolism plays in either the pathogenesis or the perpetuation of this disease is not clear. Both the distribution of sodium within the body and its elimination by the kidney are altered. It has been demonstrated that patients with essential hypertension have slightly elevated serum sodium concentrations. In some subjects there is an expansion of the total body sodium, and it has been postulated that this excess sodium is located intracellularly. The arterial wall of both hypertensive patients and animals is reported to contain an increased amount of sodium and water. This abnormality might be responsible for causing the elevation of blood pressure either by narrowing the arteriolar lumen or by increasing the reactivity of its smooth muscle.

The administration of sodium chloride to rats produces hypertension,⁷ while the blood pressure of hypertensive dogs and man may be reduced in some cases by a low sodium diet.^{8, 9, 10} The efficacy of the rice diet is probably due to its low sodium content.¹¹ The tenacity with which the kidney retains sodium often prevents effective depletion by the use of sodium-restricted diets. The frequent injection of organic mercurial drugs accelerates sodium depletion and lowers the blood pressure.¹² Such treatment is not practical for the long-term management of patients with essential hypertension.

Chlorothiazide is a nontoxic, potent, oral natruretic agent which may be given daily for prolonged periods of time and would appear to accomplish greater sodium depletion than can be achieved by a low sodium diet. This drug reduces the blood pressure in essential hypertension when given alone or in combination with other drugs. Our experience confirms the fact that it is an effective diuretic and antihypertensive agent. A similar hypotensive effect in the rat may be secured with other diuretic agents. When

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chlorothiazide is combined with a low sodium diet in the treatment of essential hypertension a reduction in blood pressure may be observed (figure 1 A). It may also enhance the antihypertensive action of reserpine (figure 1 B).

When chlorothiazide and ganglionic blocking agents are administered simultaneously, a synergistic action is unmistakable.¹⁴ The requirement for ganglionic blocking drugs is reduced by about one-half when the patient is receiving as little as 0.5 gm. of chlorothiazide twice daily (figure 2 A). Furthermore, patients who have undergone sympathectomy as long as seven years previously show an enhanced responsiveness to chlorothiazide administration, so that it is possible to omit the use of ganglionic-blocking drugs completely in controlling the blood pressure of some sympathectomized

hypertensive subjects (figure 2 B).

The mechanism which brings about these hypotensive effects is of great interest. The fluid and sodium depletion induced by chlorothiazide and a low sodium diet may result in a lowered blood pressure in a fashion similar to the addition of mercurial diuretics to a low salt diet.¹² This seems to be the most probable explanation of the enhanced responsiveness of the blood pressure to ganglionic blockade after chlorothiazide therapy. When circulating fluid volume is depleted, an increase in sympathetic vasomotor tone is one of the physiologic mechanisms for preventing a fall in blood pressure. A reduction of 250 to 500 ml. of blood volume by phlebotomy has been reported to produce an excessive fall in blood pressure in the presence of sympathetic blockade.¹⁷ Chlorothiazide administration has been shown to cause an acute depletion of the plasma volume.¹⁸ This appears to be a reasonable explanation of the blood pressure reduction observed when this drug is given to a patient who has been sympathectomized or is under the influence of an autonomic blocking agent.

In addition, it is possible that the drug exerts a depressor action by some other mechanism. It is not a direct vasodilator since, in our experience, the injection of 500 to 1,000 mg. of chlorothiazide intravenously has no effect on the blood pressure over the subsequent three to four hours. There is some evidence that the delayed reduction of the blood pressure may be related to redistribution of sodium within the body, rather than to the external loss of sodium chloride or water, since weight loss may not parallel the antihypertensive effect (figures 1 A, B). This hypothesis is further strengthened by the observation that the chronic administration of chlorothiazide may not cause a measurable decrease in extracellular fluid volume or sodium space. It must therefore be concluded that chlorothiazide may reduce blood pressure in some cases by depleting plasma and extracellular fluid volume and, in other cases, perhaps by an effect on sodium and water

distribution within the body.

It is difficult to reconcile these numerous observations that suggest the importance in the hypertensive state of an abnormal sodium distribution within the body with the often recorded fact that hypertensive individuals

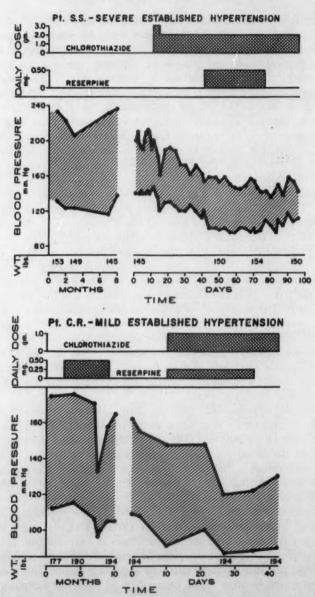
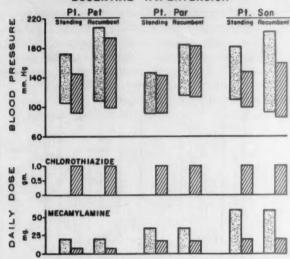


Fig. 1. The effect of chlorothiazide with and without reserpine in the treatment of patients with severe essential hypertension (A, above) and mild essential hypertension (B, below). Note change in time scale from months to days. No loss of weight occurred with the administration of chlorothiazide in spite of the reduction in blood pressure. The severely hypertensive patient showed a decline in blood pressure on chlorothiazide alone. Further lowering of the blood pressure took place when reserpine was administered. The mildly hypertensive patient who had been relatively unresponsive to reserpine initially had a good antihypertensive response when both drugs were given. The possibility that the reduction in blood pressure was due solely to chlorothiazide cannot be excluded.

ESSENTIAL HYPERTENSION



POST SPLANCHNICECTOMY

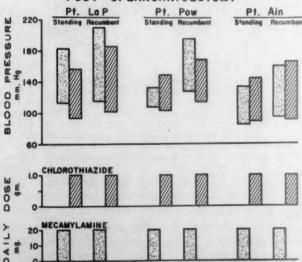


Fig. 2. The effect of chlorothiazide on the control of the blood pressure of three patients receiving mecamylamine (A, above) and three patients also previously splanch-nicectomized (B, below). For each patient, standing and recumbent blood pressures are shown with values before (stippled bars) and after (diagonally lined bars) chlorothiazide administration. Patient LaP had been splanchnicectomized three years, patient Pow six years, and patient Ain seven years previously. The addition of chlorothiazide allowed the dose of mecamylamine to be cut in half in the patients with essential hypertension and eliminated entirely in the splanchnicectomized subjects.

actually excrete more of a sodium chloride load than do normotensive subjects. 20, 21 They also eliminate a greater urine volume in response to hypertonic saline or other osmotic loads. 22, 28 The primary mechanism involved in this renal abnormality appears to be an increased tubular rejection of sodium, chloride and water. 24 On the basis of experiments with rats, it has been postulated that the hypertensive animal or patient preserves a relatively hypertonic internal environment by rejecting in the urine proportionately more water than sodium. 25, 26 In a study of the excretory response to a sodium chloride load of patients having varying degrees of hypertension,

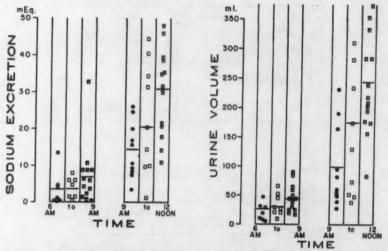


Fig. 3. The sodium (A, left) and urine volume (B, right) excreted in the three hours before (6 a.m. to 9 a.m.) and after (9 a.m. to 12 noon) an intravenous load of 2.5% sodium chloride (500 ml./1.73 M.³ body surface area given between 9 and 10 a.m.). Each symbol represents an individual and horizontal lines, group means. The 10 normotensive subjects (●) had a mean blood pressure of 108/67 mm. Hg; the eight mildly hypertensive patients (□) 155/100 mm. Hg; and the 11 moderately severely hypertensive patients (□), 175/116 mm. Hg. The direct relationship between the blood pressure and the increased excretion of both sodium and water after the intravenous salt load is evident.

the validity of this concept was suggested by the inverse relationship between the specific gravity of the urine and the blood pressure. Thowever, a further analysis of these data fails to support such a hypothesis. There is a direct relationship between the mean rate of sodium excreted and the mean blood pressure (figure 3 A). A similar correlation between the mean urine volume and the mean blood pressure is present (figure 3 B). However, if one examines the sodium excretion per unit volume of urine, there is no evidence that water excretion occurs in excess of that of sodium (figure 4). There is no direct relationship between the sodium concentration in the urine and the blood pressure under these conditions. These

data fail to support the view that a "relative retention" of sodium exists in the hypertensive subject given a salt load. Indeed, since an isolated normal kidney shows an increase in both the amount of sodium excreted and the urine volume when there is an increase in the arterial perfusion pressure, 28 it would appear that the altered renal responses are the result rather than the cause of hypertension.

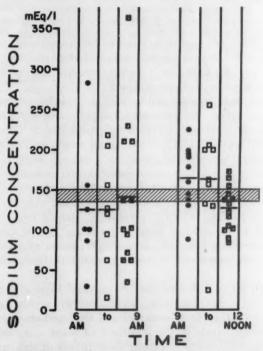


Fig. 4. The sodium concentration in the urine before (6 a.m. to 9 a.m.) and after (9 a.m. to 12 noon) an intravenous load of 2.5% sodium chloride. Symbols are identical to those in figure 3. The diagonally lined area encloses the normal range of the plasma sodium concentration; values below this represent the urinary loss of less sodium than water ("relative sodium retention"), and values above, the loss of more sodium than water. Other constituents of each solution have been disregarded. It is evident that elevation of the blood pressure does not correlate with the excretion of urine which is hypotonic in respect to sodium.

The following working hypothesis is suggested concerning these abnormalities of sodium metabolism. In some cases of essential hypertension the sodium content of certain compartments or tissues, possibly including vascular smooth muscle, may be increased. This may or may not be sufficient to elevate total body sodium as measured by conventional technics. However, it is reflected in a slight elevation in the serum sodium level in some hypertensive individuals. If there is a greater sodium and water

content of the vascular smooth muscle in the hypertensive patient or animal, this may be associated directly or indirectly with an increase in the total peripheral resistance. The ability of chlorothiazide, when used alone, to reduce the blood pressure of some hypertensive patients is perhaps the result of its depleting these tissues of sodium. This might explain its antihypertensive effect in those cases where no reduction in extracellular fluid volume has occurred.

SUMMARY

Sodium chloride metabolism in essential hypertension is abnormal. Patients with essential hypertension may have a slightly elevated serum sodium concentration, expanded total body sodium content, and increased amounts of sodium and water in their arterial wall.

Hypertension may be alleviated by sodium depletion. Chlorothiazide, a potent natruretic agent, may exert an antihypertensive effect in both hypertensive animals and patients. This drug potentiates the effect of various antihypertensive regimens. The concomitant administration of chlorothiazide reduces the requirement for ganglionic blocking drugs in the treatment of hypertension. Sympathectomized patients are unusually responsive to the blood pressure lowering effect of chlorothiazide.

The increased renal tubular rejection of sodium, chloride and water in response to salt loading, which is present in essential hypertension, is felt to be the result of the elevated blood pressure and not its cause. There is no evidence that water excretion, occurring in excess of sodium excretion, causes a "relative retention" of sodium in the majority of hypertensive

patients.

The hypothesis is discussed that in essential hypertension the sodium content of certain compartments or tissues, possibly vascular smooth muscle, may be increased and lead to the elevation of the blood pressure. The effectiveness of chlorothiazide in the treatment of some cases of hypertension might be through its ability to deplete these tissues of sodium; in other instances it appears to act through depletion of the plasma volume.

SUMMARIO IN INTERLINGUA

Le metabolismo de chloruro de natrium in hypertension essential es anormal. Patientes con hypertension essential pote haber levemente elevate nivellos de natrium seral, un augmentate contento de natrium in le corpore total, e augmentate concentra-

tiones de natrium e de aqua in le parietes arterial.

Hypertension pote esser alleviate per un depletion de natrium. Chlorothiazido, que es un potente agente natriuretic, es capace a producer un effecto antihypertensive tanto in animales hypertensive como etiam in patientes con hypertension. Iste droga produce un potentiation del effectos de varie regimes antihypertensive. Le administration concomitante de chlorothiazido reduce le requirimento de drogas de blocage ganglionic in le tractamento de hypertension. Patientes qui ha essite sympathectomisate responde usualmente al action reductori que chlorothiazido exerce super le tension del sanguine.

Es opinate que le augmentate rejection de natrium, chloruro, e aqua, per que le tubulos renal reage a cargas de sal in hypertension essential, es un effecto e non un causa del elevate tension de sanguine. Il existe nulle prova que le excretion de aqua, occurrente a grados in excesso del excretion de natrium, causa un "retention relative" de natrium in le majoritate del patientes con hypertension.

Es discutite le hypothese que in hypertension essential le contento de natrium in certe compartimentos o in certe histos—possibilemente le lisie musculo vascular—es augmentate e resulta in un elevation del tension del sanguine. Il es possibile que le effecto de chlorothiazido in le tractamento de certe casos de hypertension depende de su capacitate de privar tal histos de natrium. In altere casos le effecto de chlorothiazido pare producer se per le depletion del volumine de plasma.

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BENIGN FAMILIAL ICTERUS: A REPORT OF THREE CASES*

By S. Ross Fox, Jr., M.D., Seattle, Washington

Benign familial icterus is a clinical entity, not infrequently encountered, that is often confused with hemolytic disease, biliary tract disease, and disease of the liver. For this reason it deserves discussion. The purpose of this paper is to substantiate further the observation that the disorder tends to be hereditary. Three patients, a father and his two sons, are discussed.

CASE REPORTS (Laboratory Results Table 1)

Case 1. A 22 year old white Coast Guardsman was admitted on July 2, 1956, complaining of jaundice of two and one-half years' duration. Scleral icterus was first noted by the patient's mother after he returned from several weeks at sea, during which time he was quite seasick. No choluria, acholic stools, abdominal pain, diarrhea, constipation or pruritus was noted at the time. The jaundice spontaneously subsided over a period of three or four days.

Recurring episodes of icteric sclerae followed, occurring every two to three months and lasting three to four days. These bouts usually followed upper respiratory tract infections, episodes of overexertion, emotional stress or excessive intake of alcohol. The appearance of the jaundice was accompanied by mild malaise and anorexia, but no nausea, vomiting, diarrhea or abdominal discomfort.

The patient gave no history of exposure to jaundiced persons or to sick animals. His alcohol intake was moderate and his diet adequate. His work had brought him into contact with some paint, paint solvents and small amounts of carbon tetrachloride. He had noted no food incompatibilities, postprandial distress or bloating.

During the course of his stay in the Coast Guard he had received the usual immunizations. He had donated blood on several occasions but had never received a transfusion. Three units of his blood had been given to patients over the previous two years without untoward reaction.

The patient's past medical history was significant only in that he had had an appendectomy one year prior to admission and at that time his bilirubin was found to be elevated (2.06 mg. per 100 ml.). There was no family history of icterus except for the patient's maternal grandfather, who was jaundiced terminally with carcinomatosis.

Physical examination revealed icteric sclerae and a questionably palpable liver. There was no enlargement of the spleen or lymph nodes. Vital signs were normal, as was the remainder of the examination. (Laboratory studies in table 1.)

A diagnosis of benign familial icterus was made. Investigation of other members of the patient's family revealed his father and his younger brother to have an elevated serum bilirubin. His mother and sister had no hyperbilirubinemia.

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TABLE 1

0.2-1.0 0.1-0.4 0.1-0.6 40-54 15.0 5-10,000 5.0-5.5	7.7 0.6 7.1 47 17.4 5,700 Normal 5.69 1.6% Start Complete .44 .30 .44 .34 Negative 0.2	2,6 1.0 1.6 48 16.8 5,400 Normal 5.6 2.8% Start Compl 44 .30 .46 .38 Negative	12.7	.46 .3	plete
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	0.84 1.72 2.56				
1-8	hepatic tissue was				
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	normal pigment.	1			
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		Normal		Normal	
	Normal				
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Case 2. A 46 year old white retired Coast Guardsman, father of case 1, was admitted to the hospital on September 11, 1956, complaining only of epigastric burning, intermittent and mild in nature, of four years' duration. The discomfort was always relieved by food. He gave no history of jaundice, food incompatibility, acholic stools, choluria, pruritus, diarrhea, constipation, nausea, hematemesis or melena.

Physical examination was unremarkable except for a slight yellowish discoloration of the sclerae. (Laboratory studies in table 1.) The liver and spleen were not palpable. X-ray examination revealed a duodenal ulcer. Anticholinergic medications caused complete remission of symptoms.

Case 3. A 20 year old Coast Guardsman, brother of case 1, gave no history of jaundice, abdominal pain, acholic stools, choluria or pruritus. His alcohol intake had been moderate, his diet good. He had not knowingly been exposed to any hepatotoxins. No food incompatibilities had been noted. His health in general had been excellent.

The physical examination revealed no abnormalities. (Laboratory studies in table 1.)

Laboratory results in all three cases revealed an elevated serum bilirubin, mostly of the indirect fraction, without evidence of a hemolytic process. The fecal and urinary urobilinogen excretions were normal, as were the reticulocyte counts, the peripheral blood smears, the osmotic fragilities and the Coombs' tests. In the first patient the bone marrow showed mild erythroid hyperplasia. This was probably secondary to the withdrawal by venipuncture of 150 ml. of blood for tests prior to the sternal aspiration.

Radiologic studies of the gall-bladder performed on cases 1 and 2 showed no abnormalities, and there was no symptomatic evidence of cholecystitis or cholelithiasis in any of the three cases. Aside from the hyperbilirubinemia, conclusive evidence of hepatocellular dysfunction was absent. In cases 1 and 2 there was a marginally elevated bromsulfalein retention, and in case 1 a 4 plus cephalin flocculation. Bilirubin tolerance tests performed on two of the three patients showed prolonged retention in case 1 and a normal retention in case 3. In the absence of evidence of excessive blood destruction, biliary tract dysfunction or hepatocellular disease, a diagnosis of benign familial icterus was made in all three cases.

DISCUSSION

Benign familial icterus, described by Gilbert in 1907,¹ is seemingly transmitted as a mendelian dominant trait. Both sexes are affected similarly, and there is no demonstrable predilection for any ethnic group. The disorder is most commonly discovered in young adults, though it may appear at any age. Persons so affected give a history of intermittent bouts of jaundice, with partial or complete disappearance of icterus during remissions. The exacerbations are related to emotional stress, excessive fatigue, intercurrent infections, gastrointestinal dysfunction or, occasionally, to alcohol intake. Frequently the episodes are accompanied by mild malaise and mild anorexia. Several authors ^{2,8} have commented on the "extraordinary monotony" of fatigue and asthenia along with jaundice as the presenting complaints. Clinical icterus may be entirely absent, as noted in cases 2 and 3 described in this paper.

Laboratory studies show the serum bilirubin to be elevated. The van den Bergh partitioning of the pigment indicates the indirect fraction to be high, while the direct fraction is normal or minimally elevated, rarely over 1.0 mg. per 100 ml. Intravenous injection of exogenous bilirubin shows retarded excretion. (Fifteen per cent retention in four hours is normal.⁴) Other liver function studies are usually normal. A marginally elevated single test may be found, as in the first patient, whose cephalin flocculation persistently ranged from 3 plus to 4 plus, all other tests being within normal limits. Liver biopsies on persons with this disorder show no micro-

anatomic changes of the hepatic structures, no excessive cellular pigment or abnormal fibrous tissue.

The urinary and fecal urobilinogen, reticulocyte count and bone marrow studies are seldom abnormal, indicating the absence of hemolysis. The peripheral blood smear shows no significant changes. The erythrocyte osmotic fragility is not increased, and the direct and indirect Coombs' tests are normal.

Gall-bladder disease is seldom suspected from either the laboratory studies or the radiologic examinations. Rosenthal, Comfort and Snell ⁸ found that cholecystic disease existed in 30% of their 60 reported cases. Other observers have failed to confirm this.

The laboratory studies, when all are considered, give no evidence of significant hepatocellular disease, biliary tract dysfunction or hemolytic disease in benign familial icterus.

In contrast to this benign type of hereditary icterus, Crigler and Najjar have reported seven cases of "congenital familial non-hemolytic jaundice with kernicterus." None of these patients gives evidence of hemolytic disease or primary biliary obstruction. Severe central nervous system disease is usually present, and the condition is most often fatal. These workers have concluded that the hereditary trait is recessive in this disorder. All but one of the patients were the descendants of a common ancestor. The prognosis in this disease is poor, differing from Gilbert's simple familial cholemia or benign familial icterus.

Dubin ⁷ and Sprinz ⁸ have described an entity similar to Gilbert's syndrome but with microscopic evidence of hepatocellular change. Their cases had persistent hyperbilirubinemia, with the serum bilirubin approximately evenly divided between the direct and the indirect fractions. Liver biopsies showed heavily pigmented hepatic cells. Studies on the particles in the cells revealed a lipochrome-like pigment. These patients had some malaise, abdominal pain, and alteration of their liver function tests, which do not usually occur in benign familial icterus. No familial tendency has been demonstrated. Frequently there is x-ray evidence of gall-bladder disease.

Reichman and Davis ⁹ have observed that a persistent indirect hyperbilirubinemia may follow an episode of viral hepatitis for an indefinite period of time. Liver biopsy does not indicate residual fibrosis, and apparently the course is benign.

Gilbert's disease is benign, familial, and manifested by mild to moderate indirect hyperbilirubinemia; the three patients described have this disorder. The Crigler-Najjar syndrome is typified by intense icterus from increased indirect bilirubin, symptoms of central nervous system disease, and an almost invariably fatal outcome. It, too, is hereditary. The Dubin-Sprinz type of disorder is not familial, and there is evidence of pigment deposition in the hepatic cells. Finally, a posthepatic indirect hyperbilirubinemia has been observed by Reichman and Davis in a few patients.

Several theories have been advanced concerning the etiology of benigh hyperbilirubinemia. Dameshek and Singer ¹⁰ have suggested that the disorder is a disturbance of the permeability of the hepatic cells to the passage of bilirubin. They feel that the pigment is of the indirect type because it fails to gain access to the liver cells and hence is retained in the blood stream. Childs and Najjar ¹¹ postulate that the direct-reacting bilirubin is a metal chelate of the indirect-reacting bilirubin. The chelation is accomplished by an enzyme normally present in the hepatic cells. A relative or absolute deficiency of this enzyme accounts at least in part for the hyperbilirubinemia found in physiologic jaundice of the newborn, Crigler-Najjar disease, and possibly in Gilbert's syndrome.

Billings has suggested, and recently Schmid ^{12, 18} has demonstrated, that after the cyclic heme molecule has been opened the liver attaches two glucuronide radicals to the compound. The solubility of the substance is thereby increased, allowing the liver to excrete the bilirubin. Glucuronic acid is moderately abundant in hepatic tissue because it is an intermediary compound in the metabolism of glucose, and also is a component of many polysaccharides in the body. Numerous substances are detoxified by the liver through conjugation with glucuronic acid. These reactions are seemingly fostered by specific enzymes.

Benign familial icterus might well represent a decreased ability of the liver to conjugate indirectly reacting bilirubin with glucuronic acid due to a specific enzyme deficiency. Patients with this disorder seem to have a "decreased hepatic reserve." The liver can process the normal amounts of bilirubin quite adequately, but any condition which causes an increase in the amount of bilirubin or a minimal decrease in the excretory capacity of the liver causes the appearance of jaundice. This postulate would explain the prolongation of the bilirubin tolerance test usually demonstrable in this disorder. It would also explain the "threshold effect" noted by Comfort. 14, 15

In the benign form of hereditary hyperbilirubinemia the enzyme is probably present but in diminished amounts. Patients with the Crigler-Najjar syndrome have been demonstrated to have absolute enzymatic deficiency. In these individuals the serum bilirubin levels range from 27 to 45 mg. per 100 ml.

The prognosis in the Crigler-Najjar type of disorder is poor. Only two reported patients with this syndrome have not shown the symptoms of kernicterus. They usually die in infancy. Therapy is futile, for the etiology of this disease is an enzymatic deficiency. Enzyme replacement in this disorder has not as yet been accomplished.

The prognosis in the Dubin-Sprinz syndrome is favorable, though there is microscopic evidence of hepatocellular change. In benign familial icterus the prognosis is excellent. No therapy is indicated. Patients with this disorder should be advised to avoid those things which precipitate exacerbations.

SUMMARY

Three cases of benign familial icterus are presented, a father and two sons. This further confirms the observation that a hereditary tendency exists in this disorder. The condition is believed to be an inborn enzymatic deficiency resulting in the inability of the hepatic cells to conjugate indirectly reacting bilirubin with glucuronic acid. There is no hepatocellular change microscopically, as there is in the Dubin-Sprinz syndrome, and the course is benign, as opposed to that seen in Crigler-Najjar disease. Correct diagnosis of benign familial icterus is important because it simulates serious diseases. If unrecognized, unnecessary surgical and medical procedures may be performed and needless restrictions may be imposed upon the patient.

ACKNOWLEDGMENTS

Dr. David D. Kliewer and Dr. James G. Telfer contributed valuable suggestions and encouragement, both appreciated by the author.

SUMMARIO IN INTERLINGUA

Benigne ictero familial es un entitate clinic que simula frequentemente morbo hemolytic, morbo del vias biliari, o morbo hepatic. Es presentate tres casos—de un patre e su duo filios—que demonstra un tendentia hereditari in iste disordine. Il pare que illo es transmittite como dominante mendelian.

Patientes qui suffre del condition hic discutite presenta un historia de episodios intermittente de jalnessa in que le exacerbationes es precipitate per stress emotional, excessos de fatiga, infectiones, dysfunction gastrointestinal, o ingestion de alcohol.

Le examine physic es usualmente intra le limites del norma, con le exception del ictero, sed isto non es necessarimente apparente ab le puncto de vista clinic.

In partitionar le bilirubina seral secundo van den Bergh, on trova que le fraction indirecte es elevate durante que le fraction directe es normal o minimalmente elevate. Le concentration urinari e fecal de urobilinogeno, le numeration reticulocytic, e studios del medulla ossee es usualmente normal. Le frottis de sanguine peripheric es normal, e le mesmo vale pro le fragilitate osmotic del erythrocytos e pro le tests de Coombs. Studios del vesica biliari es usualmente normal.

Studios del function hepatic es rarmente anormal, excepte le test de tolerantia pro bilirubina. Isto revela communmente un retention prolongate del bilirubina a reaction indirecte.

Studios laboratorial resulta in nulle indication de significative morbo hepatocellular, dysfunction del vias biliari, o de morbo hemolytic.

Multe theorias ha essite formulate con respecto al etiologia de benigne ictero familial. Recentemente il ha essite demonstrate que post que le molecula cyclic de heme se ha aperite, le cellula hepatic attacha duo radicales glucuronidic a ille composito. Isto augmenta le solubilitate del substantia, e le hepate es capace de excerner lo.

Benigne ictero familial es ben interpretabile como effecto de un reducite capacitate del parte del hepate de conjugar bilirubina a reaction indirecte con acido glucuronic, e iste reducite capacitate esserea le effecto de un specific carentia enzymatic. Il es possibile que le tendentia de disveloppar un tal carentia es transmittite geneticamente.

Le prognose in iste disordine es semper favorabile.

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PSYCHOSOMATIC RESEARCH: PROBLEMS IN **METHODOLOGY***

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WITH the publication of The Influence of Psychologic Factors Upon Gastrointestinal Disturbances, by Alexander and his group 3 in 1934, psychosomatic research seemed to be at the door of a new era. This was the first widely accepted analytic investigation delineating a relationship between emotional states and the physiologic function of an organ system. It seemed only a question of time until much greater advances could be made. 23 years later, psychosomatic research is still hesitating at the threshold. I would like to examine some problems which have impeded its progress.

"Scarcely can we have a morbid affection of body in which some feeling or function of mind is not currently engaged directly or indirectly as cause or effect," wrote Sir Henry Holland in 1852. A century later Alexander 2 reëmphasized that every disease is psychosomatic, with organic and emotional factors varying in importance from case to case, perhaps even in the same disease. "Psychosomatic medicine" was conceived as a method of approach. Unfortunately, in our culture words soon become entities themselves in place of the idea which they were meant to convey. Consequently one finds in current journals references to the "psychosomatic illnesses." By and large this term refers to the group of illnesses listed in medical texts 15 years ago as "diseases of unknown and doubtful etiology." Psychosomatic research has been almost limited to poorly understood clinical syndromes, where pathophysiology is not well known. Since the modern phase of psychosomatic research is concerned with a more exact delineation of the effect of psychologic events upon physiologic processes, and since the latter are themselves only slightly known in the illnesses under investigation, the number of variables is almost endless and the result of investigation is mainly conjecture.

Conceiving "psychosomatic illness" as separate from other illnesses leads to intellectual pitfalls in other ways. Recently the author of a study on hyperthyroidism attempted to have a control group in regard to sociologic and emotional characteristics of the individual patient. He therefore selected a group of 25 patients with infectious hepatitis. To his dismay he discovered that 18 of the 25 had a history of an acute emotional disturbance just prior to the onset of their hepatitis. To control his controls, he se-

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lected 10 patients with pneumonia, then 10 with acute appendicitis—the findings were almost identical with those of the hepatitis patients. He wrote, "The mere presence of environmental handicaps, emotional problems and antecedent distressing emotional experiences in any patient group cannot be considered evidence or proof that these factors necessarily bear any etiologic relation to a pathological state. On the other hand this study does not exclude the possibility of such a causal relationship, the proof of which would have to be sought by other means." ²¹ So much for those non-psychosomatic illnesses! But in pneumonia, for example, is it not possible that emotional states alter the immune antibody response, which could account for the "resistance of the host" (a threadbare expression which could use some investigation) varying among exposed people? ^{4,7,17,22} Unfortunately, since these illnesses are traditionally considered nonpsychosomatic, they have been virtually outlawed from psychosomatic research.

One of the main obstacles in research has been the disinterest of the general medical profession, so that most psychosomatic investigation has been left to psychologists, psychiatrists and their ancillaries. Moreover, the general medical profession seems unwilling to accept psychologic evidence as objective, reliable data. Are these physicians merely reactionary, as those unconvinced of the earth's roundness even after the Great Voyages, or has the nature of psychosomatic research until now helped create such

skepticism?

By and large the traditional psychosomatic illnesses are chronic and remittent, and have only partially effective symptomatic treatment. There is a tendency for the attending physician to cull out of this group those patients obviously disorganized psychologically, those who are becoming no better or perhaps getting worse with supportive medical management, those whose defenses are not consonant with the physician's (and thus "abnormal"), and those who are dissatisfied in some way with their treatment. These are exiled to the psychiatrist. Because of the severity and chronicity of most of these illnesses (and for other reasons), many of these patients have socio-economic problems and find their way to low cost clinics, especially those connected with university medical schools, where much research is conducted. This sampling is also weighted by the number of passiveaggressive and dependent people who find a haven with nonservice-connected illnesses in veterans' hospitals, where generalizations are frequently drawn on "psychosomatic patients." Further distorting the sampling is the fact that much research is done with the severely ill, bed-ridden patient whose ego is much weakened under the impact of his illness and its implications. Previous major defenses of the personality (such as compulsive hard work) may be shattered by the enforced incapacity. The outpatient bears little resemblance usually to his defense-threatened and ego-weakened counterpart lying in bed. Every physician knows the tremendous difference between the appearance and reactions of a peptic ulcer patient, for example, who

comes into the office for a six-month check-up and those that are manifested as he lies in unrelieved pain or in massive hemorrhage. Equally dramatic is the difference in the colitic, asthmatic or arthritic patient during periods of activity and quiescence of illness. With these distortions in sampling, it is small wonder that investigators entertain the possibility of "the existence of a distinguishable psychosomatic personality per se" 18-18—this peculiar breed being characterized as shy, withdrawn, seclusive, cycloid, flighty and unstable, more socially passive, lacking in confidence, feeling inadequate and inferior, easily distracted, irritated and annoyed.12 The private physician, reading this and comparing these characteristics with those of his own patients with similar physical illnesses, is entitled to be amused, or worse, to shrug off psychologic research as nonsense. His contempt is increased upon reading research papers explaining somatic processes as though they were psychic ones, similar to hysteric conversion phenomena. While with some sophistication we can laugh at the outdated concepts of the 1920's, when fever was equated with sexual excitement, and increased blood flow to an organ viewed as a displaced erection, there still appear articles with similar ideation—for example, the weeping lesion of a dermatitis signifies weeping for the lost mother. While depression might play an important role in the production of a skin lesion, it is asking too much of sebaceous glands and dermal capillaries to make associations and to express affect. As has been so well understated elsewhere. "Some of the theories proposed by psychiatrists do not inspire confidence in the mind of the physiologist." 24 Psychosomatic theory must be consonant with known physiologic mechanisms, or formulate new theoretic neurophysiologic causal explanations. To do less, to propose theories based on a mystic kind of symbolism alone, is to strain the credulity of the reader.

The actual method of research approach leads to another set of problems. Investigations have been confined, with a few notable exceptions, to specific clinical entities (a group of epileptics, a group of migraine patients, etc.), rather than to broad physiologic or biochemical measurements. But what is a clinical entity? Is it a constant from patient to patient? Does ileitis¹ = ileitis² = ileitis^{*}? Or may this arbitrarily created "entity" vary as to etiology and course? And what is ileitis? What is rheumatoid arthritis? It has reached such a point that specialty societies have laid down rules-one is not permitted to have "rheumatoid arthritis" unless he possesses seven of a dozen or so criteria. An allergic reaction is "nonallergic" when there is an absence of family atopy and no demonstrable reagins. True, there is merit in attempting to separate illnesses which might resemble one another clinically. What we now recognize as pneumonia, typhoid and influenza were all lumped as "fevers" at one time. On the other hand, it has become de rigueur to separate two "entities" rather arbitrarily, such as migraine versus tension headache, when the pathophysiology of neither is really known. Might they not represent

similar processes with slightly different clinical manifestations? Moreover, when individual diseases are studied, the course of the illness is used as the sole indicator of responses to psychologic events, well or ill. Can this be an accurate validation, however, when variables are so poorly controlled? Might not the particular response be to a stimulus unknown to the investigator? It is always easy, though not always accurate, to pin responsibility in retrospect onto a specific conflict or situation or affect— post hoc ergo propter hoc. But even if the response really does follow the psychologic stimulus the investigator recognized, he is still confronted with the "how" of it.

The political aphorism that all men are created equal does not apply to man's organs and vegetative nervous systems. Yet traditionally they are considered as such. By and large, organs are considered to be normal or diseased, and these findings are confirmed patho-anatomically. Usually the function of an organ is tested by comparison with that of another man's, instead of with its own at a different time and under other conditions. If one found identical pepsinogen levels in 100 people, one might draw the erroneous conclusion that this represented equivalence. In reality this would represent the peak output of some individuals and minimal function of others. while the rest would represent varied percentages of capacity to function. "Normal" is a distribution curve, psychologically and physiologically. The quantitative potential of organ systems of individuals must be studied over a period of time before any correlation can be established with emotional states. And these correlations must be made in the intact functioning organism before much can be made of such correlation in the sick one. These measurements should not be confined to the organ system giving symptoms. Until now, who has been interested in the gastric function of a patient with a respiratory disease, or vice versa? Unfortunately, much of the otherwise excellent correlative research done recently has suffered from a marked inequality in the respective depth of physiologic and psychologic data and inexactness of measurement of the latter. While a micrometer was applied physiologically, a crude yardstick was used psychologically. No effort was made to obtain unconscious material, and the investigators were satisfied to report those conscious factors, the awareness of which they shared with the patient. The recent work of Margolin 18 has well demonstrated that not only is there a marked variance between the observable and unconscious affect of the individual, but that there also may be even a major change in concept of body image from moment to moment not observable without analytic investigation. In any event, investigation could be applied more fruitfully to physiologic and biochemical determinants (such as the concomitants of affects) rather than to specific "diseases."

There has been a tendency for investigators, especially in psychiatric settings, to separate their research cases from their treatment cases. This

has evolved partly from the isolation of groups of patients with the same disease entity, a factor mentioned previously. However, the separation goes beyond that of specific disease study, and concerns the interpersonal relationship of the patient and his therapist, which is altered for the research patient. The research patient is chosen for study, not usually by his motivation for seeking psychiatric help, but by the psychiatrist's interest in the particular illness. Indeed, many patients are funneled by other clinics regardless of their wishes. Since many are unwilling, or at best reluctant, concessions are granted in order to placate them. For example, the fees are frequently reduced for the research case. If the research patient is seen over a period of time, the investigator has a considerable investment in him and can ill afford the patient's dropping out. This frequently leads to his having a different attitude toward his research patient than toward his other cases, resulting in transference and counter-transference problems difficult to manage and with data difficult to evaluate. Even more commonly, however, the research patient is seen for only a tiny fraction of the time a treatment case is usually studied. Under these conditions, no matter how intensely the psychologic data are pursued, no matter what testing or projective technics are used as adjuncts, no matter how skilled the observations and integration of the investigator, the psychologic data will be of limited value. There is no way to validate such material, nor can any but crude formulations be drawn of personality structure, dynamics, or response to conflicts. This is said not to minimize the importance of such investigation, for such surveys of the field are often urgently needed as pilot studies, but only to point out its limitations, especially when pursuit of specific mechanisms is involved.

Most investigators seem to be searching for a unitary factor which will be applicable to the causality of all "psychosomatic illness." Depending upon the year each was fashionable, we have seen examination of the personality structure, perusal of defenses, study of the nuclear conflict, difficulty in communication, and, more recently, a reëmphasis on the importance of mood and affect. There is a tendency to reject that which is not ubiquitous. It is most likely that these factors play a varying role from one disease to another, and should not be discarded because they do not apply equally to all. Just as the etiology of an infectious disease (measles) differs markedly from a deficiency disease (pellagra), so might be the case in those illnesses with large emotional components. The production of simple symptoms from different psychologic sources—direct expression of emotion or conflict, the incidental effects of such expression, or the effects of acting out-has been well documented already.²⁸ Similarly, one man's pneumonia may result from an encounter with an extremely virulent organism, that of a second from a poor immune-antibody response as a consequence of chronic alcoholism, and that of a third from unnecessary exposure in a neurotic acting out, etc. Once again, only when pathophysiology is better understood can such formulations be made for each case.

Whatever direction psychosomatic research takes, it is apparent that major advances will require combined psychic and somatic investigation. Since so few individuals are competent in all spheres—clinical medicine, clinical psychiatry and psychoanalysis, biochemistry, neurophysiology—a team approach seems the best hope for a breakthrough. A team can function only with the mutual respect and understanding coöperation of each of its members.

SUMMARIO IN INTERLINGUA

Le presente articulo examina certes del problemas que ha impedite progresso in le recerca psychosomatic. Un del principal obstaculos es le erronee notion que solmente certe morbos—per exemplo arthritis, colitis, asthma, e ulcere peptic—es psychosomatic plus tosto que *omne* morbos. Per consequente, multe recerca es guastate in le investigation de pauco comprendite syndromes, durante que morbos de melio comprendite pathophysiologia es negligite.

In plus, certes del medicos qui es le melio qualificate pro effectuar recercas psychosomatic es sceptic in le presentia de datos psychologic. Illes se senti discoragiate per conclusiones psychologic de character semi-mystic que es frequentemente contrari a cognoscite factos physiologic e per le presentation de patientes psychosomatic como un racia peculiar e distincte, lo que non es de accordo con le experientia del medico mesme. Distorsiones in le selection del casos, que es le base de tal conclusiones, es discutite.

Certe problemas del methodologia recercatori es examinate, principalmente le problemas inherente in le selection del casos, le assecurantia del datos, e le urgentia de effectuar un standardisation. Es proponite que on debe observar le effecto del emotiones super le processos physiologic e biochimic plus tosto que le rolo del emotiones in specific entitates pathologic. Iste effectos debe esser correlationate in subjectos normal durante prolongate periodos de tempore ante que le signification del datos pote esser evalutate in patientes con anormalitates physiologic. Es discutite le inequalitate del mesuration psychologic e del mesuration physiologic in le recerca de nostre dies. Le idea que un sol factor pote esser incriminate cosmo causa de omne morbo es characterisate como questionabile.

In conclusion, le desiderato de un attacco multidisciplinari in le recerca psychosomatic es presentate urgentemente. Lo cooperation que es recommendate debe esser basate super un respecto mutual e un comprension reciproc inter le varie brancas del medicina.

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REVIEW

RUSSIAN RESEARCH ON ARTERIAL **HYPERTENSION***

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I. INTRODUCTION

As elsewhere, arterial hypertension has been a subject of extensive research in the U.S.S.R. In contrast to the continuing controversy about etiology and pathogenesis of essential hypertension outside the Soviet Union, in the Russian literature of the last two decades the basic ideas concerning this disease have been strikingly uniform. Essential hypertension ("hypertensive disease") is regarded, in principle, as a cardiovascular neurosis. Alterations originating in the cerebral cortex produce first labile and later stable elevation of blood pressure, with secondary renal and cardiac involvement. At the same time it is recognized that a number of endogenous and exogenous factors contribute to the development and manifestations of the disease.²⁻⁸

In the Russian literature the cortical origin is not postulated for essential hypertension alone; it is assumed also for some other internal diseases, for instance, gastric ulcer. The assumption is based on Pavlov's general view that the cerebral cortex controls the activity of all internal organs. Emphasis on the role of the cerebral cortex for normal physiologic regulations, and their disturbances in pathologic states is characteristic of the recent Russian literature in all fields of medicine.

Pavlov's original work on conditioned reflexes was essentially limited to the salivary and gastric secretion. In reviewing the experimental investigations of M. K. Petrova, M. A. Ussievich and of other collaborators and successors of Pavlov, Ivanov-Smolensky ⁷ (p. 138) concludes that they "showed convincingly that functional pathological states of the higher parts of the brain, caused in animals by collisions, overstrain of nervous processes and nervous breakdowns, are manifest not only in derangement of their external behavior, but also in various profound changes in the internal medium of the organism, in the functioning of the internal organs, in the vegetative functions, thus embracing the whole organism."

By far the largest amount of work in this direction was carried out by K. M. Bykov and his associates, who enlarged considerably the experimental basis of Pavlov's concept of corticovisceral interaction. They obtained conditioned reflexes of various autonomic functions by the association of unconditioned responses (such as diuresis on water ingestion, hypoglycemia after insulin, hyperglycemia and increase of blood pressure after adrenalin, etc.) with optic or acoustic signals. The conditioned reflexes changed in various types of pathology, and the unconditioned reactions were changed by stimulation of the cerebral cortex. Lesions of the cerebral cortex were found to affect the development

of experimental pathologic states. This line of work has been continued and

further expanded.

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It is hard to visualize from the outside the tremendous impact of Pavlov's work and concepts on the present Soviet biologic and medical literature. There is hardly a medical paper without some reference to Pavlov. Over 400 papers on Pavlov from 1949 to 1952, and 335 from March, 1953, to April, 1954, were listed in two editorials of the Journal of Physiology of the U.S.S.R.^{9, 10} They included papers by the most prominent authors in all medical fields, even so remote from Pavlov's original work as otolaryngology or obstetrics. Emphasis on the role of the central nervous system (C.N.S.), particularly the cerebral cortex, as etiologic factor is a part and parcel of the general picture of present medical research in the U.S.S.R., and the application of the theory of "nervism" to arterial hypertension was only a question of time. Lang is credited with being the first one to present, in 1948, a rounded and integrated view of arterial hypertension based on Pavlov's concept, in a paper read at the Academy of Medical Sciences.¹¹

Against this background, it is understandable that Lang's extensive monograph, "Hypertensive Disease," 1 was readily accepted from the moment of its publication (1950). It has served as the basic reference book and a guide for most of the work on arterial hypertension since then, and it is considered to be a classic work on this subject. It provided the most thorough documentation for a neurogenic theory of pathogenesis, which most authors in the U.S.S.R. seemed to anticipate before it was fully formulated. Lang suggests that arterial hypertension is initiated by disturbance of the normal regulatory (inhibitory) effect of the cerebral cortex on the hypothalamic vasomotor centers. The resulting increased excitability of the vasomotor centers exaggerates pressor responses, first producing periods of transient increase of blood pressure, due to spastic contractions of arterioles. Renal, cardiac, cerebral and endocrine involvement is considered to be secondary, but of increasing importance in the later phases of hypertension. The initial cerebral cortical disinhibition results from prolonged psychic stress, particularly suppressed "negative" emotions. The emphasis on the role of psychic trauma in the etiology of essential hypertension is, of course, not new, nor is it limited to the U.S.S.R. In regard to case studies and the use of anamnestic data, the Russian literature is indeed similar to the psychosomatic literature elsewhere. The main contribution of the Russian authors to our knowledge of essential hypertension is their attempt, on an unprecedented scale, to obtain experimental, objective evidence for the significance of the central nervous system in the etiology and pathogenesis of arterial hypertension.

It is intriguing to compare Lang's with Pickering's outstanding monograph on the same subject.¹² Since Lang's book was not known to Pickering, each monograph is an independent critical review of the same field, of nearly the same size (about 500 pages). In regard to essentially all factors involved and hypotheses advanced, except the involvement of the cerebral cortex and excitability of the vasomotor centers, both authors agree that none explains adequately the etiology and pathogenesis of arterial hypertension. Pickering holds that this is true also for involvement of the cerebral cortex and the vasomotor centers, in contrast to Lang's concept. On careful reading of Lang's monograph, it appears to the present reviewers that Lang was less critical in regard to C.N.S.

involvement than he was in his criticism of other hypotheses. However, as it turned out, all further work in the U.S.S.R. has supported Lang's view, and today its experimental and clinical basis is considerably larger than in 1948,

when it was first presented.

It may be noted that the different emphasis on the role of the central nervous system is not the only difference between Pickering's and Lang's approach. Perhaps still more important is the fundamental concept of arterial hypertension. All publications in the U.S.S.R. use the term "hypertensive disease," which implies a qualitative, pathologic difference between "normal" and "elevated" blood pressure. The term "essential hypertension" is rejected by Russian authors because it expresses the lack of knowledge of its etiology. Since the Russian authors believe they have clarified the etiology, the expression "hypertensive disease," as a clinical entity, seemed to be justified. Pickering advances important considerations and facts for a quantitative rather than a qualitative difference. Research in the U.S.S.R. up to the most recent publications has taken for granted that arterial hypertension is a disease, while this important problem of quantitative vs. qualitative differentiation should be an important subject for further research. In clinical application, this means that in the initial phase hypertension is diagnosed as a disease before it clinically qualifies as such. It is not certain that clinical disease actually develops in all cases thus diagnosed.

In spite of its one-sided emphasis, the large material accumulated in the U.S.S.R. deserves serious consideration in the ultimate synthesis and integration of information on this important topic. We have attempted to survey the Russian literature with emphasis on experimental work and on the novelty of information, considered against the background of available material accumulated outside the U.S.S.R. However, specific references to work outside the U.S.S.R. have been kept to the bare minimum. Russian work on the clinical aspects, including drug therapy, is largely omitted, because it duplicates, more or less, known information. The selection of the material is therefore somewhat arbitrary; it does not represent a true cross-section, and the bibliography is selective

rather than complete.

It may be mentioned that Russian medical terminology, starting from different basic concepts, is not always readily comprehensible. The reviewers have here and there taken some liberty with the Russian terms in an attempt to express their meaning, since verbal translations might have been misleading.

II. CLASSIFICATION

Lang's ¹ (p. 336) classification of the stages of "hypertensive disease" is generally accepted in the U.S.S.R. It will be presented at the outset for the reader's orientation. In principle, Lang's classification of "hypertensive disease" follows the time-honored chronologic division into prehypertension, labile hypertension and fixed hypertension. There is, however, an important difference, in that these stages are identified with specific etiology or pathology.

To facilitate the differentiation between the stages, a detailed description of their characteristics is given, including subjective symptoms, blood pressure, cardiac, cerebral and renal symptoms, eyegrounds and histopathologic changes. A prodromal stage, characterized by hyperreactive responses of the blood pressure to emotional and a variety of sensory stimuli, is followed by the first, or

neurogenic stage, which is subdivided into two phases: (a) temporary arterial hypertension, and (b) permanent, but unstable increase of blood pressure, with occasional decreases to normal level. In the second, or transitional, stage, the blood pressure is higher and more stable, typical hypertensive headaches are present, together with slight or moderate cardiac decompensation, left ventricular hypertrophy, angina pectoris and cerebral angiospasms, but renal involvement is absent or slight. The third, or nephrogenic, phase is characterized by stable, high blood pressure, renal insufficiency, and increasing cardiac and cerebral pathology. Malignant hypertension is not regarded as a separate chronologic

phase but as an aggravated third stage.

Well-founded objections to this classification were made by Miasnikov. 18 The development of pathologic lesions and of clinical symptoms does not follow such rigid patterns as is assumed in Lang's classification. C.N.S. involvement is present throughout the entire course, not only in the first stage; renal involvement may occur quite early but, on the other hand, it may be absent in hypertensive patients who die from cardiac or cerebral complications. Cardiac and cerebral involvement also varies widely in different patients in regard to the time course of the disease. Miasnikov suggests a differentiation between (a) "hypertensive disease," originating from disturbance of cortical and subcortical vasomotor regulation, and (b) symptomatic hypertension. This is similar (though reversed in order) to Pickering's 12 classification into secondary hypertension and essential hypertension. In Miasnikov's system, (a) (hypertensive disease) is subdivided into three chronologic stages: Stage I, phase a: prodromal; phase b: transitory increases of blood pressure; Stage II, phase a: labile hypertension; phase b: stable hypertension; Stage III, phase a: sclerotic degeneration, compensated; phase b: decompensated. This classification incorporates the essential elements of Lang's classification, the main difference being that the pathogenic identification is omitted. An additional code characterizes cardiac, renal, cerebral or combined involvement, independent of the chronologic sequence of development.

Tsinamzgvarishvili ¹⁶ also differentiates between hypertensive disease (essential hypertension) and symptomatic (secondary) hypertension. Hypertensive disease is subdivided again into three chronologic stages: Stage I a, prodromal; I b, manifest but unstable hypertension; Stage II a, stable-reversible; II b, stable-irreversible; Stage III, decompensated. The use of reversibility as a criterion

of classification appears to be highly questionable.

Miasnikov's classification appears to be superior, but Lang's system is still preferred by the large majority of Russian authors. In view of the overlap of symptoms in the various stages, the classification, except for the late stage, is somewhat arbitrary, and the grouping of patients by different authors would probably not be identical in regard to the various stages and phases. The greatest objection may be directed against the definition of transient blood pressure increase as the first stage of "hypertensive disease," because "hypertensive disease" is diagnosed as present before it actually has developed. Not all persons who are hyperreactive or who have transient elevated blood pressure develop stable arterial hypertension.

Miasnikov ¹⁸ considers the universal acceptance of Lang's classification as an advantage over the lack of such agreement outside the U.S.S.R. Since the same criteria are used, comparison of different groups is facilitated, and the descrip-

tion of symptoms characteristic of the different phases of arterial hypertension is condensed by just referring to the various stages by number, or in terms of underlying functional disturbance (neurogenic, nephrogenic). Since Lang's classification rests on assumptions which are still subject to further research, the advantage of universal acceptance may be temporary.

III. CENTRAL NERVOUS SYSTEM INVOLVEMENT IN THE PATHOGENESIS OF ESSENTIAL HYPERTENSION

The most convincing evidence for primary central nervous system involvement in the etiology of essential hypertension would be an objective demonstration of disturbance of C.N.S. functions prior to the development of arterial hypertension. This would require a longitudinal study on a large group of initially "normal" people, a substantial proportion of whom may be expected ultimately to develop essential hypertension. No such investigation seems to have been carried out.

In the absence of such evidence, the idea of primary C.N.S. involvement would be supported by (1) production of stable arterial hypertension by electrical, mechanical or chemical stimulation, trauma, or pathology of the C.N.S.; (2) production of stable arterial hypertension by experimental functional C.N.S. disturbances in animals; (3) disproportionate incidence of psychic stress and emotional trauma in individuals who develop essential hypertension; and (4) demonstration of C.N.S. disturbances in the early phases of essential hypertension.

1. C.N.S. stimulation and trauma. Numerous clinical observations on blood pressure increase in various lesions of the brain have been reported ¹² (p. 119). The Russian literature in this field goes back as far as 1871, when Ovsiannikov (quoted by Miasnikov, ¹⁶ p. 22) found that stimulation of the medulla oblongata increased the blood pressure. Danilevskii (1875, ¹⁶ p. 23) obtained pressure reactions by mechanical stimulation of subcortical parts, and Bechterew and Mislawsky ¹⁷ by electrical stimulation of the motor and premotor zones of the gyrus praecentralis in cats and monkeys. More recently, Koreisha ¹⁸ observed pronounced and sometimes prolonged increase of blood pressure in man during brain surgery upon irritation of the middle hypothalamic region. Of interest is also Koreisha's observation of regional contralateral hypertension in patients with cortical and subcortical brain tumors, in agreement with earlier animal experimental material.

These findings were confirmed by Baliasnyi. In lesions of the cortical motor zones an increase of the blood pressure on the contralateral side occurred frequently. In most patients with hemiplegia the blood pressure was significantly higher on the side of hemiplegia, and this asymmetry was more pronounced in hypertensive than in normotensive patients. The blood pressure was also unilaterally higher in hypertensive patients with some disturbance in the pyramidal pathways but without gross cerebral lesions. Gurvich 200 found that the repeat variability of blood pressure increased on the paralyzed side in 25 out of 38 hypertensive patients with hemiplegia, particularly in the early phase of the cerebral hemorrhage. In nine patients the difference of the blood pressure between the right and the left arm exceeded significantly the normal limit of 5 mm.

Il'ina 20b found in epileptic attacks produced in dogs by electrical stimulation

of the brain an increase of the blood pressure in the carotid artery up to 300 mm. Hg. The increase occurred within two to five minutes of the stimulation, and the elevation of the blood pressure continued for several hours. In Pentothal anesthesia the attacks were milder, and no increase of the blood pressure

developed.

Application of powdered foreign material to the dura mater in dogs produced arterial hypertension for from two to four months (Borshchevskii, quoted by Kondratovich, ²¹ p. 7). This type of experimental hypertension is similar to that produced by cisternal application of kaolin. ²² All of these observations have relevance for secondary central hypertension, but not necessarily for essential hypertension. The same is true for the role of cerebral ischemia, which may be responsible for the appreciable incidence of arterial hypertension in patients

with mitral stenosis 1 (p. 123) and pulmonary emphysema.

Miasnikov 28 attaches greater significance for the pathogenesis of essential hypertension to experiments by Keiser,24 who produced arterial hypertension in dogs for several weeks or months by means of cerebral concussion, in the absence of gross brain damage and cerebral hemorrhage, and in the absence of changes in the cerebrospinal fluid. Control experiments with abdominal trauma failed to produce arterial hypertension. Anesthesia during cerebral trauma diminishes or prevents the increase of blood pressure. Removal of the kidneys, but not of the adrenals, several hours before the cerebral concussion prevented the arterial hypertension. Without paying attention to the blood pressure, Ivanov-Smolenskii 25 found previously that cerebral concussion first produces increased cortical and subcortical excitability, followed by inhibition. This is the same mechanism that, according to the majority of Russian authors, is involved in the pathogenesis of essential hypertension. In this connection, it is of interest that Andreev 26 obtained conditioned pressor reactions using weak blows against the head as unconditioned stimulus. Miasnikov therefore considers the post-concussion hypertension to be a true link to essential hypertension in man, 16 (p. 50) in that cerebral concussion only initiates the development of hypertension; the further course of the disease has no direct relationship to the extent of the brain lesion. Should this hypothesis be correct, one might expect a large incidence of arterial hypertension in patients with postconcussion syndrome. While elevated blood pressure is quite common in acute head trauma, it is not conspicuous in the postconcussion syndrome. Clinical experience therefore does not seem to agree with Miasnikov's suggestion.

Stimulation of the posterior region of the hypothalamus in rabbits by means of small inserted electrodes increased the blood pressure by from 30 to 50 mm. In these animals, various weak sensory stimuli, applied simultaneously with direct hypothalamic stimulation, which were without effect in normal animals, produced pronounced pressor responses. These responses increased on repetition of stimulation.²⁷ This is quite similar to the situation in patients with essential hypertension who respond with pressor reactions to a variety of stimuli

which do not change the blood pressure in normal subjects.

2. Production of arterial hypertension by experimentally induced functional disturbance of the C.N.S. Production of arterial hypertension in animals by inducing disturbances of the C.N.S., in the form of "experimental neurosis," appears to be the most powerful argument in favor of the potential significance of the C.N.S. for the pathogenesis of essential hypertension. In contrast to other

types of experimental hypertension, the mechanism of blood pressure elevation induced by C.N.S. factors a not predetermined by the experimental procedure as such (deafferentiation or renal ischemia), and has to be explored in reference to specific functions and organs. This situation is in some respects similar to that present in essential hypertension in man. The first step, of course, would be the demonstration that chronic arterial hypertension can be produced in this way. Audiogenic hypertension in dogs 28 shows that unusually strong sensory stimuli may produce prolonged arterial hypertension. However, unusually strong sensory stimuli are not conspicuous in the history of patients with essential hypertension, nor is the incidence of arterial hypertension in people exposed to excessive acoustic stimulation.298

Gefter et al.29c produced stable hypertension in rats by continued electrical pain stimulation.

Of greater significance would be the production of stable arterial hypertension by conditioned signals; this experimental situation would be closer to that which may (as is frequently maintained in psychosomatic literature) lead to the development of essential hypertension. This would apply particularly if not excessively strong unconditioned stimuli were used. The reservation should be made, however, that the biologic strength of a stimulus is determined not only by its physical properties but also by its biologic significance, which varies widely from species to species, and by the physiologic state of the organism, especially the excitability of the autonomic centers and of the hypothalamus.29b

In the extensive Russian literature on conditioned reflexes and production of experimental neurosis in the dog, reports of arterial hypertension have not been conspicuous until recently. This might be due in part to the fact that attention had not been focused on the blood pressure. Chernigovskii and Iaroshevskii 30 found in one dog an increase of the blood pressure from 135-140/75-90 to 240/150 mm. of Hg during the development of experimental neurosis produced by conflicting conditioned signals. The blood pressure remained elevated for five months, but returned to the initial level after the experiment was discontinued. In another dog with reflexes conditioned to an acoustic signal associated with weak electrical skin stimulation, a single strong electrical shock was given together with the acoustic signal. After that, the acoustic signal produced elevation of the blood pressure up to 280/170 mm. of Hg for several weeks, although the strong electrical shock was not repeated.

Chernov 31 applied daily electrical skin stimulation above the pain threshold in dogs and noticed a gradual increase of the blood pressure. Bringing the dog into the laboratory raised the blood pressure by 30 to 60 mm., even before the onset of electrical stimulation. The same author also obtained in rats pressor reactions to electrical skin stimulation associated with acoustic or optic conditioned signals. In these experiments, however, acute pressor reactions rather than stable hypertension were produced. Prikhodkova, Omelchuk and Khaleva (quoted in 21, p. 32), using conflicting conditioned signals, observed rather prolonged elevation of the blood pressure in dogs.

Usievich 38 produced stable hypertension in dogs with "weak" C.N.S. (according to Pavlov's classification) by switching excitatory and inhibitory conditioned signals. Similar results were reported by Strakhov 84 and by Iaroshevskii.85 Gavlichek 86 produced hypertension by applying simultaneously a positive and an inhibitory conditioned signal, and compared the effect of switching conditioned signals in dogs with various "types" of C.N.S. The increase of blood pressure was most pronounced and prolonged in the "excitable" type.

Prikhod'kova and Zol'nikov 87 were also able to develop stable hypertension in dogs with experimental neuroses produced by conflict situations. Sodium bromide decreased the blood pressure to normal in spite of continuation of conflicting conditioned signals. Of particular interest are the experiments of Napalkov and Karas. 88 because they not only produced arterial hypertension in five dogs by means of conditioned signals, but also abolished it by change of the conditioned activity. They used strong unconditioned stimuli producing a significant transient increase of blood pressure, such as pain resulting from electrical skin stimulation, exposure to a cat, pistol shots, lifting by the legs up to 3 meters, etc. The systolic blood pressure increased under the impact of these stimuli up to 160 to 180 mm. Conditioned signals obtained on this basis produced a greater increase of the blood presure than did the unconditioned stimuli (up to 220 to 240 mm. of Hg). While extinction of conditioned reflexes usually occurs after about 10 to 20 repeats without reinforcement, the exaggerated conditioned pressor response was maintained even after 900 repeats without reinforcement, carried out during a period of one and one-half months. At the same time, all earlier conditioned reflexes involving feeding as unconditioned stimulus disappeared and, together with the neurosis, a stable arterial hypertension developed. Even after the experiments were discontinued the hypertension was maintained for the total length of observation (five months).

The arterial hypertension could be abolished by the following procedures:
(a) presentation of a similar but weaker signal, not associated with the unconditioned stimulus, gradually brought up to the strength of the previous conditioned signal producing the pressor response; (b) a strong stimulation of different sensory receptors; and (c) association of the conditioned signals producing the pressor response with feeding instead of the strong unconditioned stimuli used before. The abolition of experimental hypertension by change of the conditioned activity is an excellent confirmation of the causal relationship in this experimental

situation.

Makarychev and Kuritsa 89 produced a conditioned acoustic pressor response to adrenalin injection in three dogs after 12 repeats. On this basis, a gradual increase of the blood pressure developed within 18 months, exceeding, at the end of this period, the initial blood pressure level by from 30 to 60%, and associated with eyeground changes similar to those observed in essential hypertension in man. In this study no experimental neurosis was involved, which is an important difference from production of arterial hypertension by means of conflicting conditioned signals. The arterial hypertension produced by Makarychev and Kuritsa is of some interest in view of reports of increased adrenalin in the blood in essential hypertension, which is, however, a controversial subject inside and outside the U.S.S.R. Buguslavskaia 40 found increased adrenalin, while Spivak 41 and Zhislin and Smazhnova 42 found no correlation between the content of adrenalin or catecholamines and essential hypertension. The conditioned arterial hypertension does not prove that adrenalin is involved in essential hypertension, but it does show the potential involvement of the cerebral cortex together with hypertensive effects of humoral factors.

Andreev, Vadkovskaia and Glebova 48 associated conditioned acoustic signals with subcutaneous renin injections in dogs, which produced an immediate increase

of the systolic blood pressure by from 50 to 100 mm. Hg for from four to six hours. The conditioning experiments were performed daily for a prolonged time. Conditioned pressor responses were obtained with this procedure. These observations suggested that the cerebral cortex may be involved, at least under special experimental circumstances, in the mediation of the effects of renin. This is, however, not proof of etiologic involvement of the cerebral cortex in the

action of renin in essential hypertension.

According to large-scale research at the Medico-Biological Station in Sukhum, the monkey appears to be the ideal animal for study of neurogenic hypertension. The normal range of blood pressure was determined in over 3,000 measurements on 200 monkeys (baboon, rhesus and others).44 The normal systolic blood pressure varied from 115 to 135 mm., and the diastolic from 65 to 85 mm. Hg. It increased with age (from the first to the fifth year) by 10 mm. for the systolic and 5 mm. for the diastolic blood pressure. The blood pressure of baboons was higher than that of other monkeys. The average daily range of variation of the systolic blood pressure was 16 mm., that of the diastolic 12 mm. Hg, with the minimum at 4 a.m. Of particular interest is the observation of spontaneous hypertension in 14 monkeys. 44, 45 Three years later the series was increased to 300 monkeys, 46 which did not change the normal range obtained in the smaller series. Out of the 300 monkeys, 20 were found to be hypertensive. Further observation revealed that in six animals the arterial hypertension was transient and in 14 permanent. The latter animals developed changes of the eyegrounds, left ventricular hypertrophy and left ventricular strain pattern in the electrocardiogram, typical for essential hypertension in man. According to the authors, spontaneous arterial hypertension in monkeys is in all details identical with essential hypertension in man. Apparently, however, no detailed pathologic study of the hypertensive animals was made. Some of the animals were autopsied, but their number was not given and the published autopsy data are scanty. It appears that secondary hypertension was not safely ruled out, at least not for some of the animals.

In five normotensive animals, experimental neurosis was produced by conflicting conditioned signals. 46, 47 The first disturbance of the blood pressure was a change in the pattern of diurnal variations 48a; later, the response to the cold pressor test became exaggerated, and pilocarpine produced an increase instead of the normal decrease of blood pressure. Several months after the development of neurosis, arterial hypertension developed (systolic pressure up to 180-220 mm., diastolic up to 110-120). In several animals the hypertension was transient, in others it was maintained for up to two years. In the latter animals, secondary eyeground and electrocardiographic changes compatible with ischemic heart disease developed; however, there was no correlation between electrocardiographic changes and blood pressure. (Neither is there such a correlation in human hypertension.)

Figure 1 shows the development of experimental hypertension in three monkeys, parallel to the development of experimental neurosis. It is of interest that a slight hypotension precedes the increase of blood pressure. Figure 2 shows the development of arterial hypertension in another monkey, together with the decline of other conditioned reflexes, indicating a deep disturbance of cortical activity. Interesting as the results are, their significance is limited by

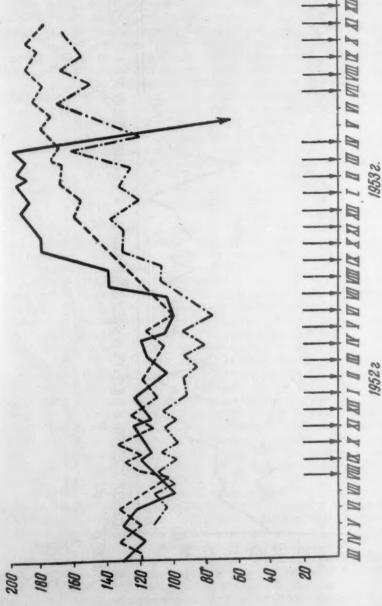


Fig. 1. Development of arterial hypertension (ordinate: systolic blood pressure, mm. Hg) in three monkeys during the development of experimental neurosis produced by conflicting conditioned reflexes elicited at times indicated by arrows on the base line. The abrupt fall of blood pressure in one of the monkeys is premortal (Magakian et al.,46 figure 3).

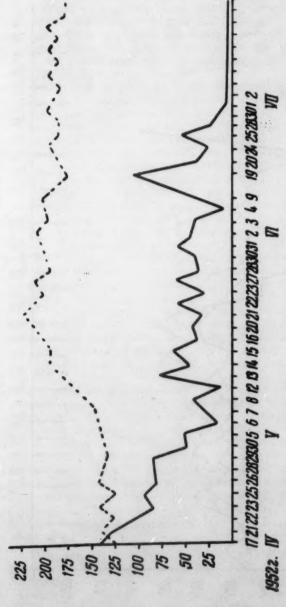


Fig. 2. Development of arterial hypertension in a monkey with experimental neurosis, associated with a decrease of positive conditioned motor responses (solid line); broken line: blood pressure (Mininoshvili et al.,47 figure 6).

the small number of animals. Nevertheless, these results show that monkeys are susceptible to arterial hypertension following functional C.N.S. disturbance.

The positive results of producing stable arterial hypertension by conditioning show that disturbance of cortical regulation may be etiologically involved in the development of essential hypertension. It is strong supporting evidence for the development of essential hypertension on an emotional basis, cited in numerous case reports, but it does not conclusively prove that this is the dominant

etiologic factor in all cases of essential hypertension.

3. Psychic stress and emotional trauma. Among Russian clinicians, G. F. Lang has insisted since 1922 on the importance of prolonged psychic ("nervous") stress and so-called "negative" emotions (fear, anger, resentment) in the development of hypertensive disease. He was quite outspoken on this point in his 1950 monograph. The "neurogenic" theory of the origin of essential hypertension, including the idea that psychic stress and emotional trauma represent a dominant factor, is now generally accepted in the Soviet Union. The Russian authors 16 (p. 43) regard as the basic factor the disturbance of the cortical processes, a "neurosis" in I. P. Pavlov's sense, i.e., disturbed relations between cortical processes of inhibition and excitation, their concentration and irradiation, their intensity and stability. Hypertensive disease is the consequence of this kind of disturbance, which may, according to Pavlov, be brought about by excessively strong or complex stimuli, overstraining of the inhibitory processes, or by the conflict of inhibitory and excitatory processes. In man, the significance of the role of verbal stimuli ("second signal system") and of psychologic stresses is interpreted as pointing to the involvement of cortex. F. A. Andreev, in considering the importance of interpersonal relations and situational conflicts—in the family, at work, in the community—referred to hypertension as the "most human of all diseases that affect man" 16 (p. 55).

It may be noted that Wolf et al., 48b in their summary of some 10 years of

It may be noted that Wolf et al., 48b in their summary of some 10 years of investigative work on circulatory adjustments to life experiences, are very cautious regarding the mechanisms involved in pressor responses to difficult life situations and in the pathogenesis of essential hypertension. These are their conclusions regarding life stress: "Not only may the hemodynamic changes characteristic of hypertension, including a reduction in renal blood flow, be induced for short periods in suitably susceptible persons by the contemplation of stressful life experiences, but long-term variations in blood pressure level have been repeatedly correlated with periods of stress. Moveover, the data indicate that the course of essential hypertension may be mitigated by measures directed at enhancing the satisfactions and improving the adjustment of the individual" 48b

(p. 231).

The number of case reports by Russian authors concerning exaggerated pressor reactions initiated by emotionally charged situations is large, and both the procedures and the results are similar to those reported in the psychosomatic literature outside the U.S.S.R. A detailed review, therefore, does not appear to be needed. Of greater interest are data on the relative incidence of "stress" in individuals who develop hypertension, blood pressure responses in the presence of emotions, the problem of individual reactivity to stressful stiuations, and effects of occupational stresses,

(a) Life stress and hypertension. One of the crucial questions, still not settled satisfactorily, is the relative incidence of psychic stress and emotional

trauma in individuals who develop essential hypertension. Tolubeeva and Flegontova, 40a co-workers of G. F. Lang, examined systematically anamnestic data obtained in 200 hypertensive patients and 100 normal individuals (controls). Reëxamination of the data indicated statistically highly significant differences for the acute emotional trauma (30% vs. 10%) for "negative" emotions (55%

vs. 11%) and for prolonged emotional trauma (68% vs. 25%).

The situation is complicated by the fact ¹⁸ (p. 44) that unpleasant experiences are not the only kind of emotions associated with a rise in blood pressure; "positive" emotions may also elicit marked pressor reactions. However, these are acute effects. The role of positive emotions in the genesis of essential hypertension remains to be clarified. Furthermore, the Russian workers tend to put all of the "negative" emotions into a single basket, disregarding for the most part the possibility that different negative emotions may have quite different physiologic effects ^{29b} (p. 157). Parasympathetic effects are dominant in anxiety and hostility, sympathetic effects in fear ^{49b} (p. 129).

As to anamnestic data, one cannot neglect the possibility that they may be unwittingly influenced by the interviewer and distorted by the person interviewed. Patients' interpretations of their past life experiences tend to be colored by the very presence of the disease. The weakness of this method and the difficulties of describing premorbid personality on the basis of data obtained from hypertensive patients are well illustrated by the controversy regarding the "nervous type" of the individuals who are likely to develop hypertensive disease.

(b) The problem of "types." This "stress" of life situations involves interaction between the individual and his environment. The fact that responses to identical environmental and interpersonal situations differ in different individuals is interpreted by the Russian experimentalists and clinicians in terms of the "types" of central nervous system and higher nervous activity. Pavlov developed the concept and criteria of the "types" in the context of animal experimentation. The properties of higher nervous activity that constitute "type" are (1) the strength of the processes of excitation and inhibition (weak type, with heightened susceptibility to inhibition, vs. strong type, resistant to exhaustion and the resulting protective inhibition); (2) equilibrium of the processes of excitation and inhibition (impetuous, unequilibrated type, with predominance of excitatory over the inhibitory processes, vs. equilibrated type, able to develop readily both positive and inhibitory conditioned responses); and (3) mobility (lively type, adapting easily to changes in the environment, vs. quiet type, characterized by a relative inertness of the basic cortical processes of excitation and inhibition). The extreme types are the weak inhibitory and the strong excitable type; the labels "lively" or "quiet" distinguish the two varieties of the strong equilibrated type 50 (p. 111f). The strong, balanced type is characterized by the strength of the basic nervous processes, greater effectiveness of protective compensatory and adaptive mechanisms and, consequently, greater capacity for the restoration of disturbed functions.

Chernorutskii, 51 in a paper summarizing some seven to eight years of work at the Institute of Physiology of the Academy of Sciences, admits that scientific research on the subject of "types" in the framework of internal medicine is still in its very beginnings. The methodology is in the process of development. Emphasis is on the premorbid period, using detailed (directed, depth) anamnesis. As to the frequency of occurrence of the different "types," Chernorutskii gives

no data for control groups. In five nosologic categories that were studied (hypertensive disease, ulcers, neurasthenia, bronchial asthma and rheumatism), there were no differences in the relative frequency of the "types." One positive finding was the dominance (three quarters to four fifths of the patients) of the "strong, imbalanced" and the "weak" types. The premorbid reaction pattern is reported to be associated with the clinical picture and the course of disease. There are more clearly expressed clinical symptoms and a relatively acute course in the "strong" type, and less well defined symptoms and a more chronic

course in the "weak" type.

Dreerman ⁵² also regrets the absence of adequate methods for the determination of the "type" of higher nervous activity in normal individuals or in patients. He was highly critical of clinical-experimental methods, specifically, the method of "directed speech reactions." He feels that the method, not very good for the study of people free of disease, is still less valid for getting at the premorbid typologic characteristics of patients suffering from hypertension or ulcers. He has a better opinion, in principle, of the approach based on the biographic record of behavior, together with observations made in the clinic, but believes that its application has been frequently faulty and the results have been of dubious value. He has grave doubts, in particular, about the comparability and biologic significance of the behavior of individuals living in different social environments. The author calls for systematic inventory of behavioral reactions, in specific situations, of individuals representing clear-cut, "pure" types. This information, not available at present, would then facilitate the typologic classification of behavior in a given individual.

With specific reference to hypertension, Gakkel' 58 reported from Lang's clinic that, prior to the development of the disease, the majority of the patients (80%) represented the "weak" type of higher nervous system. They were "artists" rather than "thinkers," with heightened emotionality and dominant first (sensory) "signal" system. By contrast, Kupalova et al. (cited in 18, p. 51), in their study on 150 hypertensive patients, established the presence of the

"strong" type in half the cases.

(c) Blood pressure response in the presence of emotions. Transitory changes in blood pressure of normal individuals in the presence of strong emotions are well known. The point is documented by such observations as those of Stokvis 16 (p. 39). Using a special technic for prolonged registration of blood pressure, he showed that in hypnosis it is possible to produce marked alterations of blood pressure by suggestion of fear, pain or disappointment. N. A. Tolubeeva (quoted in 16, p. 39) reported an increase in blood pressure prior to the puncture of a vein at a time when the subjects expected but did not actually feel any pain. In the moment of the venous puncture the blood pressure rose still further. N. N. Malkova 54 reported that pressor reactions during the anticipation of pain may be even greater than the response to the actual pain. In hypertensive patients the rise in blood pressure in response to emotional factors tends to be more frequent, greater and more sustained than in the control group. Both "positive" and "negative" emotions are associated with a blood pressure rise. Malkova reported in a hypertensive patient an elevation of blood pressure in response to two-hour work involving mental effort (70/40 mm.), participation in a medical consultation (80/30 mm.), the receipt of a bill (60/35 mm.) and a pleasant experience of a visit from relatives (65/20 mm. Hg).

Some hypertensive patients respond with a pressor reaction only to certain kinds of emotional stimuli which elicit, in fact, conditioned responses. In patients studied by Malkova there was a group of aviators suffering from a transient hypertension. In a pilot sent to the hospital for observation, the blood pressure rose suddenly from 150/90 to 175/110 mm. Hg when, during the physical examination, the sound of airplane motors was heard in the ward and the pilot became apprehensive and fearful as to whether he would fly again. This type of selective response to emotionally charged stimuli is considered to be typical of patients in the initial (first) stage of hypertensive disease, while generalized overreactivity to a variety of emotional stimuli characterizes later stages of the disease. In the first instance the blood pressure response is mediated by temporary associations (conditioned reflexes) that are related to the processes initiating the development of the disease, while in the latter case it points to well established, chronic processes of excitation of the vasopressor nerve centers.

Elimination of acoustic, especially verbal, stimuli produces in some of these patients a surprising lowering of blood pressure. N. K. Zamyslova ¹⁶ (p. 42) observed this phenomenon in patients placed for an hour in a silent, sound-proofed room. The blood pressure rose again upon the return of the patient to the ward. Miasnikov ¹⁶ (p. 42) stresses the repeated clinical observations that initial hypertensive reactions are frequently elicited by verbal stimuli in the form

of disturbing news, a tense discussion, etc.

(d) Occupational stress. Here we are concerned with "psychic stress," not with the effects of physical work environment in its climatic, pharmacologic or toxicologic aspects. The frequency of arterial hypertension was reported as being almost twice as high for workers engaged in occupations involving nervous tension as for those doing physical work; the reported percentages were 6.7% and 3.7%, respectively.⁵⁵ Increased arterial pressure under such conditions was noted by Il'ina ⁵⁶ and by Fogelson.⁵⁷

A detailed study on male and female telecommunication workers was made recently by Spivak.⁵⁸ The jobs are considered to involve high nervous tension. Consequently, analysis of the level of the blood pressure and of the incidence of hypertensive disease is of interest. As is unfortunately often the case in the Russian literature, the control group is characterized loosely as "a group of men and women who are not exposed to any noxious agents and who are free from

neuropsychic occupational stress" 58 (p. 197).

Average values of systolic and diastolic blood pressure in individuals with blood pressure within limits accepted as normal were given only for the women. In the female telegraph operators the means were essentially identical with those for the controls of the same age. The means of the female telephone operators were higher by 3 to 5 mm. Hg for the systolic and about 1 mm. Hg for the diastolic blood pressure. The author postulates—with not a very convincing logic—that the stress on the auditory apparatus of the female telephone operators is more severe (and, consequently, has a greater pressor effect) than is the visual work of the telegraph operators.

In regard to the frequency of elevated blood pressure, the percentages were highest for the telegraph operators (12.9% for men, 9.8% for women). They were elevated also for the telephone operators (8.6% for both sexes), as compared with the controls (4.2% for men, 4.6% for women). Size of the groups compared was not given, so that no tests of statistical significance can be per-

formed, another undesirable feature of much Russian medical and biologic

writing.

The two criteria—average "normal" blood pressure and frequency of hypertension (i.e., of blood pressure elevated above the norm)—do not fully agree in regard to the "hypertensive" nature of the two jobs. It may be noted that the female telegraph operators show absence of pressor effects on the basis of the first criterion but, at the same time, the frequency of hypertensive individuals is twice as high as in the control group. The absence of information on the mean blood pressures in normal males is especially regrettable from this point of view.

The difference in frequency of hypertension is small in younger individuals (1.8% in the combined group of female communication workers, 1.4% in the control group). It is very marked for individuals 40 years old and older (25.9% vs. 11.2%). Length of time on the job is positively correlated, at comparable ages, with increased incidence of hypertension. The author compared individuals who had held these jobs for less and for more than 10 years. The morbidity figures were 1.0% and 4.8% in the younger group. The author concludes that

occupational stress significantly influences hypertensive morbidity.

(e) Comment. Because of the central significance assigned to the disturbed function of the C.N.S. in the development of hypertension, it may be useful—at the cost of certain repetitiveness—to summarize the Russian point of view 1 (esp. p. 322). Lang 1 cites Pavlov's observations, made in the course of his studies on experimental neuroses, that under the influence of excessive nervous strain foci are formed in the cortex in which the processes of excitation become depressed or extinct. Application of the stimulus does not elicit an adequate response. Such pathologic inertness cannot be compensated for by the activity of other parts of the brain.

In man, excessive nervous strain, particularly the strain resulting from emotional trauma and presence of "negative," especially inhibited affects, weakens the functional capacity of the brain cortex. This is reflected in the decreased effectiveness of the regulatory (inhibitory) influences normally exerted on hypothalamic centers. Emotional stress results in a pathologic depression (inertness) of the processes of excitation in the higher nervous centers regulating blood pressure. Contributory factors are a "weak" type of higher nervous activity and increased reactivity of hypothalamic centers. An inhibition of the external expression of emotions tends to prolong the state of excitation of the higher autonomic centers.

On the whole, the assessment by the Russian authors of the role of emotional factors in the development of essential hypertension is much less satisfactory than in the physiologic appraisal of the changes in the central nervous system.

4. C.N.S. changes in early hypertension. In the evaluation of the significance of functional C.N.S. disturbances for the pathogenesis of essential hypertension, their appearance in time would be important as an indirect criterion for differentiation between primary and secondary C.N.S. involvement. Secondary C.N.S. involvement should be absent or infrequent in the early phase, and should increase with the exacerbation of the disease. Primary involvement should be present before (which would be hard to demonstrate) and in the earliest phase of hypertension, and would not necessarily have to increase with the clinical

progress of the disease. Secondary and primary C.N.S. involvement may produce different types of functional changes.

(a) Electroencephalogram (EEG). Khvoles and Soskin ⁵⁰ found, in the early phase of essential hypertension, acceleration and disorganization of the alpha rhythm and, later, decrease of amplitude and development of slower

rhythm; their material (28 patients) is, however, quite small.

Disturbance of spontaneous EEG activity and of the EEG response to optic stimuli was reported by Zhirmunskaya 60 in 220 patients with arterial hypertension. Five different types of EEG changes were noted, and were believed to be correlated with the clinical course of essential hypertension. A detailed description of the data would exceed the scope of this review. The author concludes that the results indicate increased excitability in the earlier phases and decreased excitability, together with the development of focal changes, in the later phases of the disease, which is in essential agreement with Khvoles and Soskin. However, Palatnik et al.61 observed decrease of the amplitude of the alpha waves in early hypertension, which is at variance with Zhirmunskaya's conclusion. In the later phases, these authors found slow delta rhythm with large amplitudes.

In the thorough studies of Il'ina and Ivannikova 62 and Speranskii 68 no correlation between EEG changes and blood pressure or clinical course was apparent. The EEG in hypertensive patients was far from uniform. Fast alpha rhythm was dominant in patients with emotional instability and excitability, changing frequently to small and irregular beta rhythm interrupted by large spikes, and different patterns were present in different leads simultaneously recorded. This was interpreted as prevalent excitation. In patients of the introvert type, slow rhythm of small amplitude was dominant, and the asymmetry between the EEG in different leads was less pronounced. This type of EEG pattern was interpreted as prevalent inhibition. Patients of an emotionally balanced type had a normal EEG. Miasnikov stresses the fact that the majority of patients with essential hypertension show definite (though not uniform) disturbance of the EEG, but concludes also that the changes appear to be related to the constitutional type of the C.N.S. rather than to the disease.

Brezhneva 64 found prevailing beta rhythm in 22 patients in the first stage of hypertension (according to Lang's classification), and irregularity interpreted as "disorganization" in 43 patients in the second stage, but the EEG of 35 patients in the third stage was normal, except for an increased reactivity to various stimuli. There was a general parallelism between EEG changes and the development of arterial hypertension in the first two stages, but not in the third one.

Results and interpretation of EEG changes in the U.S.S.R. are obviously still controversial.

Psychomotor reactions. Using motor responses to verbal signals as a criterion for the functional condition of the C.N.S., Zamyslova 65 noted an increase in the incidence of abnormal reactions in 105 patients with essential hypertension, in proportion to the severity of the disease. In the third phase of hypertension the response was considered to be "abnormal" in 90% of the patients, as compared to a 25% "abnormal" response in the control group. There was, however, a considerable age trend: in a normal group of 45 subjects over 50 years, "abnormal" responses were found in 80%. Since most patients probably were middle aged or older (the age distribution was not given), it is questionable

whether there was a significant difference between the patients and a control group of the same age. It appears also that the differentiation by means of this test is, at best, semiquantitative. However, a good agreement was claimed for verbal-motor responses, EEG, clinical data and history in regard to the characterization of the functional state of the C.N.S., particularly in patients with either little or pronounced disturbance of the C.N.S. Disagreement between these methods occurred more often in patients with dissociation of the EEG representing various cortical areas.⁶⁶

(c) Chronaxy. Motor chronaxy, particularly the difference between extensor and flexor chronaxy, has attracted attention in the U.S.S.R. because it depends on the tone of the hypothalamic sympathetic centers (Lapicque's chronaxie de la subordination). Since the sympathetic centers are involved in both vasomotor and chronaxy regulation, changes of motor chronaxy were expected in essential hypertension and an appreciable amount of material was accumulated.

A significant shortening of the motor chronaxy in early essential hypertension was reported by Kosheleva, ⁶⁷ Fisher, ⁶⁸ Il'ina ⁶⁹ and Vasilevskaia, ⁷⁰ together with a pronounced increase of the ratio extensor: flexor chronaxy. The rheobase was not essentially changed. The normal increase of motor chronaxy during sleep was significantly reduced in hypertensive patients. ⁷⁰ There was a tendency to a lengthening of motor chronaxy in the later phases of essential hypertension. ⁷⁰

The sensory skin chronaxy of 59 patients in the first two stages of hypertension was also significantly shorter. The normal increase of the skin chronaxy in darkness from 157% to 268% was reduced to 110 to 130%. Fisher found a tendency to the lengthening of skin chronaxy in the later phases of hypertension. Il'ina's 11 detailed regional study of skin sensitivity and chronaxy is somewhat at variance. In the majority of 86 patients she found no significant change of the skin chronaxy, but did find regional zones of increased sensitivity as tested with small needles.

In contrast, the optical chronaxy determined by phosphenes produced by electrical stimulation was lengthened.⁷⁰ This was more frequent and more pronounced in the third stage of the disease, but there was no definite correlation with the clinical course or the eyeground changes. The normal increase of optical chronaxy in darkness was less pronounced or absent.

Sniakin's findings 72 of disturbance in the response to darkness in hypertensive patients may be related to the prolongation of the optical chronaxy.

Zhislin and Vlasova ⁷⁸ found pronounced shortening of the vestibular chronaxy, together with right-left asymmetry, in all phases of essential hypertension but, in general, progressive with the clinical course. In the early phase the shortening of the chronaxy was variable and reversible to normal values, but became more stable in the later phases. Ageeva-Maikova ¹⁶ (p. 212) studied the effect of sympathomimetic drugs on the vestibular chronaxy. Sympathomimetic drugs sharply decreased the chronaxy, together with subjective deterioration, more so in the later phases than in the earlier phases of essential hypertension, while parasympathomimetic drugs had the opposite effect. Perhaps these results have a bearing on Zhislin and Vlasova's ⁷³ observation of pronounced decrease of the vestibular chronaxy in or shortly before hypertensive crises. The disturbance of the vestibular chronaxy in arterial hypertension was confirmed by Galvas.⁷⁴ Davidov ⁷⁸ found an increase of the vestibular rheobase

in the first stage and a decrease in later stages of essential hypertension. The findings are of considerable interest in view of the frequency of dizziness in arterial hypertension.

Disturbance of dark adaptation in essential hypertension was asserted by Sniakin. Large fluctuations of the acoustic and visual thresholds, together with disorganization of the EEG and vascular hyperreactivity, were found to be typical for early phases of essential hypertension, while in the later phases vascular hyporeactivity developed and the EEG became normal again. To

Gurevich 77 found a shortening of motor and vestibular chronaxy in dogs and

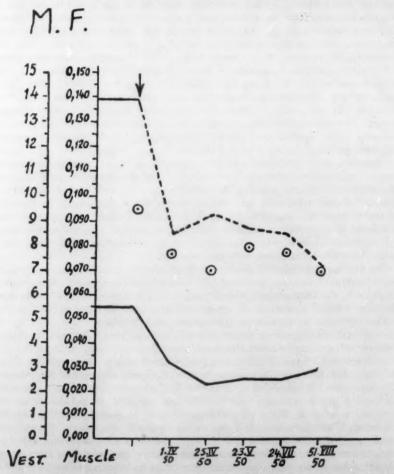


Fig. 3. Change of chronaxy in deafferentiation hypertension. Motor chronaxy (solid line: flexor; broken line: extensor) and vestibulary chronaxy (circles) of a rabbit before and after deafferentiation (arrow). Ordinate: microfarads. The systolic blood pressure before operation was 110 mm. Hg; two weeks after operation it increased to 154 mm. (Gurevich 77).

TABLE 1

Motor Chronaxy (in Sigma Units) in 11 Rabbits in Wake Condition and in Urethane
Sleep Before and After Production of Experimental Hypertension

		A. B	efore Hyperto	ension		
Conscious Condition		Urethane Sleep		Sleep Effect		
	a	ь	a'	b'	a'-a	b'-b
	Flexor	Extensor	Flexor	Extensor		
Mean	0.29	0.41	0.80	0.97	0.51	0.56
		В	. Hypertensi	on		
	c	d	c'	d'	c'-c	d'-d
Mean	0.15	0.20	0.22	0.27	0.07	0.07
		Effec	et of Hyperte	nsion		
В-А	-0.14	-0.21	-0.58	-0.70	-0.44	-0.49

(Calculated from Gurevich's Data)

rabbits in neurogenic as well as in renal experimental hypertension, starting as early as from one to three weeks after the operation (figure 3). The drop of the chronaxy was steeper in the neurogenic hypertension. In contrast to observations in patients, the decrease of the chronaxy was more pronounced in the extensors than in the flexors.

From a later series of Gurevich ⁷⁸ we calculated the statistical significance of the changes of motor chronaxy, in the conscious state and in urethane sleep, for 11 rabbits studied before and in deafferentiation hypertension (table 1). In the conscious condition the chronaxy is significantly shorter after production of hypertension. The normal lengthening of the chronaxy in urethane sleep is nearly abolished in hypertension. Therefore, the difference of the chronaxy in the animals before and after hypertension is much greater in urethane sleep. The differences of all chronaxy items between normal and hypertensive animals in table 1 were statistically significant.

The early shortening of motor chronaxy in experimental deafferentiation or renal hypertension is obviously secondary. Therefore, the findings of shortened motor chronaxy in hypertensive patients do not allow a differentiation between primary and secondary C.N.S. involvement, but show that a general disturbance of C.N.S. function is an early feature in essential hypertension. The Russian authors feel that chronaxy measurements yield valuable information on the clinical evaluation of hypertensive patients.

(d) Conditioned reflexes. In experimental hypertension produced by conflicting signals, conditioned reflexes are generally weaker and more difficult to establish, and differential inhibition is absent in dogs 70 as well as in monkeys. 47 Since disturbance of conditioned reflexes was part of the experimental procedure, alterations in conditioned reflexes are not an independent criterion of the state of the C.N.S. It is of interest, however, that conditioned salivary and motor

reflexes are also disturbed in dogs with experimental renal and deafferentiation hypertension.⁸⁰ On the other hand, in six dogs with experimental renal hypertension, vasomotor reflex responses were increased while disturbance of conditioned salivary reflexes was only occasionally observed, particularly in dogs with "weak and unbalanced" nervous systems.⁸¹

Disturbance of conditioned vasomotor reflexes was demonstrated in the essential hypertension of man, but since conditioned and unconditioned vasomotor reflexes are intimately related, both will be discussed together in a separate section

The functional significance of the cerebral hemispheres in the development of deafferentiation hypertension in dogs was shown by Shutova ²¹ (p. 40). Removal of both hemispheres does not affect the blood pressure, pulse rate or circulation time. However, unilateral denervation of the carotid sinuses produces a pronounced arterial hypertension in these animals, and after denervation of the second carotid sinus, performed one month later, the animals died with symptoms of cardiovascular insufficiency. Bilateral denervation of the carotid sinus in animals, with removal of only one cerebral hemisphere, produced arterial hypertension without cardiovascular decompensation similar to that in animals with intact brain. Obviously, the cerebral hemispheres are involved in the circulatory compensation for the loss of reflexogenic depressor zones.

An indirect demonstration of the involvement of the central nervous system is the effect of sedation (Amytal sodium, chloral hydrate) on the electrocardiograms of 40 patients with arterial hypertension. Sedation improved the left ventricular strain pattern by reducing ST depression and T inversion, and in cases with flat or low T waves their magnitude increased. At the same time, the P wave decreased. The effect on the orthostatic test was even more pronounced: sedation prevented the T inversion (the lead was not given, but probably Lead II was used). Unfortunately, the distribution of the changes was not given. It follows from the discussion that the favorable results were not observed in all patients. These results are of considerable clinical interest. ST and T changes in emotional upsets are well known. It is possible that such effects are superimposed upon an organic basis and might contribute to the ECG variability in patients. Sedation might therefore be a valuable diagnostic procedure, but Zonenreich's experiments should be repeated and the results submitted to rigorous statistical evaluation.

The material reviewed here shows early involvement of the C.N.S. in essential hypertension and in various forms of experimental hypertension. It shows, also, that stable hypertension may be produced by conflicting conditioned signals resulting in experimental neurosis. C.N.S. involvement in essential hypertension deserves further careful consideration. Miasnikov ¹⁶ (p. 204) states: "We may conclude that we are still in the very first phase of the study of C.N.S. involvement in hypertensive disease, and our data are still far from complete and adequate."

IV. VASCULAR REFLEXES

With the Russian emphasis on primary involvement of the nervous system in essential hypertension, reflex changes in blood pressure and peripheral circulation were given much attention in research and diagnosis.

1. Carotid sinus and aorta. That carotid sinus reflexes are active in essential hypertension was shown over 20 years ago by Pickering, Kissin and Rothschild.⁸⁸ Their technic of manual compression, however, was too crude for quantitative evaluation; the degree of response, and the important question regarding changes of carotid sinus reflexes in hypertension, and in particular their possible adaptation to a higher blood pressure level, remained open.¹² In the U.S.S.R. the potential involvement of depressor reflexes elicited from the carotid sinus and aorta was studied in detail in regard to the pathogenesis of essential hypertension.

Smirnova ⁸⁴ investigated histologically the nerve elements in these reflexogenic zones in patients with essential hypertension. Degenerative changes were found in the afferent nerve endings in the carotid artery and in afferent as well as efferent nerves of the aorta. Most typical was thickening of the nerve endings. These degenerative changes in the aorta, carotid and other arteries were absent in atherosclerosis without hypertension and in other diseases (Anokhina ¹⁶, p. 145). Similar degenerative changes in experimental hypertension were produced by renin injection in dogs (Bibikova ¹⁶, p. 145). Degenerative changes in nerve fibers and endings of aorta, carotid, femoral and other arteries were reported also by Mogilnitskii and Brumstein. ⁸⁵ Hyaline and fibrous degeneration in autonomic ganglia of patients with essential hypertension ⁸⁶ is of a secondary nature.

In acute experiments on rabbits, failure of the carotid sinus reflex was demonstrated in conditions which might be relevant for essential hypertension. The depressor effect produced by electrical stimulation of the sinocarotid nerve decreases or even disappears with increasing frequency (from 50 to 200 c.p.s.) or strength of stimulation. The amplitude of afferent impulses in the sinocarotid nerve decreases during prolonged high perfusion pressure applied in a carotid artery segment, isolated from the systemic circulation, not only at the peak level of pressure but also subsequently at lower pressures (100 to 180 mm. Hg). In the isolated in situ segment of the carotid artery, prolonged electrical stimulation of the aortic nerve inhibited the depressor effect of high (200 mm.) perfusion pressure, but after cessation of electrical stimulation the depressor effect was more pronounced.88

Denervation of the carotid sinus and the aortic reflexogenic zone in animals with pronounced renal hypertension produces an additional increase of the blood

pressure.21 This result is not compatible with receptor adaptation.

Local application of Novocain to the carotid sinus in dogs under ether anesthesia produced a smaller increase of the blood pressure than in animals without general anesthesia. The authors ⁸⁹ conclude that the cerebral cortex is involved in this type of acute reflex rise in blood pressure. However, this effect is probably not specific, since anesthesia tends to decrease all types of reflex activity.

Cooling of the carotid sinus in rabbits shortened motor chronaxy of limb muscles by 40% for from five to 30 minutes, and heating increased it by 100 to 180%. Denervation abolished these reactions.⁹⁰ The results are of interest because of the changes of chronaxy in arterial hypertension (see section III-4b).

In acute arterial hypertension produced in cats and rabbits by clamping the left carotid artery after preceding ligature of the right one, the pressor response to stimulation of the sciatic nerve, and even more so the depressor response to stimulation of the aortic nerves, was increased. There was no correlation, however, between the level of the arterial hypertension and the change of the pressor

or depressor response, which persisted for some time after the clamp was released and the blood pressure returned to its initial level.³¹ In chronic deafferentiation and renal hypertension in rabbits, the pressor response to vagal stimulation and the depressor response to stimulation of the aortic nerve or to inflation of the lungs were increased. In deafferentiation hypertension the increased pressor response had already developed two to four weeks after the operation (average increase, 170% after three months), slowly dropping to an average increase of 110% after 12 months, in general in parallel to the level of

the systolic blood pressure.21

In renal hypertension the peak increase of the pressor response occurred within the first month, while the peak increase of the blood pressure occurred after from four to five months. Increased pressor and depressor reflexes were also found in rabbits in an early phase of renal hypertension by Cherkasskii 91 on mechanical stimulation of the carotid sinus through pressure variation, which is a more adequate stimulus situation. The exaggerated response diminished after from four to six months. 91, 92 It is of interest that the increase of the depressor response exceeds the increase of the pressor response. The exaggeration of the carotid sinus reflexes fits into the general picture of increased sensitivity of vasomotor centers in essential hypertension. Kondratovich 98 concludes that "the strength of impulses arising in the receptors of the depressor zones as a result of the high blood pressure is not adequate to overcome the increased excitability of the vasomotor center." In addition, the normal relationship between the change of the blood pressure and the stimulus strength is missing in hypertensive animals; strong stimuli produce the same or even smaller depresso; effects than do weak stimuli (Kondratovich 21, 98).

The depressor effect of pressure increase in a segment of the carotid artery isolated from the systemic circulation was diminished by simultaneous stimulation of the sciatic nerve, ⁹⁴ which also abolished the depressor effect of pulmonary inflation. In connection with these observations, it is of interest that the depressor effect produced by electrical stimulation of the carotid sinus is diminished or abolished in cerebral ischemia (Bisov ²¹, p. 93), and this is true also for the depressor effect of aortic nerve stimulation in asphyxia (Chervinskii ²¹, p. 93). In acute hypertension produced by stimulation of the posterior-lateral hypothalamic region, the decreesor effect produced by pressure increase on the carotid

sinus is also diminished (Blinova, Aronova and Serebrianik 21, p. 94).

Small doses of adrenalin (0.1 mg.) increased frequency and amplitude or action currents in the aortic depressor nerves in rabbits, but larger doses (0.5 to 1.5 mg.) abolished the activity, after a transient increase, in spite of the increased blood pressure. These results have no immediate application to essential hypertension except that they show possible changes of aortic or carotid sinus reflexes in periods of increased adrenalin output. Possible involvement of the carotid sinus reflex mechanism in central nervous system effects on the blood pressure is suggested by Kozenko's possible observation that conditioned depressor reactions could be obtained in dogs, when an acoustic signal (conditioned stimulus) was associated with stimulation of the carotid sinus.

Possible involvement of lymph flow changes in the hemodynamics of carotid sinus reflexes is shown in Kovanov's ⁹⁷ and Vasil'chenko's ⁹⁸ experiments in dogs. The drop of arterial blood pressure during electrical or mechanical stimulation of the carotid sinus was associated with a two- to fourfold increase of lymph flow

in the thoracic duct, while acute arterial hypertension produced by unilateral compression of the common carotid artery decreased the lymph flow. It was suggested that the changes of the lymph flow facilitate the reflex by shifting of plasma from blood to lymph vessels. While the inertia of fluid shift appears too great to explain the early changes of blood pressure in carotid sinus stimulation, the changes of the lymph flow may play a secondary role in the maintenance of carotid sinus reflexes.

In agreement with the Western literature, most Russian authors are of the opinion that the pathogenesis of essential hypertension cannot be explained by a failure of the aortic or carotid sinus regulatory mechanism. However, the disturbance in the adjustment of the carotid sinus reflexes to stimulus strength is a contributing factor to the general disturbance of circulatory regulation, thus aggravating the clinical picture. Prom this point of view, it is of interest that encouraging therapeutic results were obtained by diathermy treatment of the carotid sinus zone in 22 out of 27 hypertensive patients. Prom the blood pressure dropped close to normal values, and at the same time the exaggerated vaso-constriction to local cold application (plethysmographically recorded, see section IV, 5) became less pronounced.

2. Visceral blood pressure reflexes. According to the Russian concept of the pathogenesis of essential hypertension, the exaggerated pressor responses to external and internal stimuli play an important role in the first stage of the disease. Therefore, the effect of various visceral stimuli on the blood pressure and their modification under various experimental conditions were explored as poten-

tial contributory factors in the early development of hypertension.

High CO₂ concentration in the perfusate or cooling of the nerves of intestinal loops isolated from the systemic circulation decreased the blood pressure. ¹⁰⁰ The author concluded that a flow of continuous pressor impulses from the intestinal loops is involved in the regulation of blood pressure. The pressor response to mechanical stimulation of the gastric mucosa by inflation of a balloon was abolished and later converted into a depressor response by urethane anesthesia or intra-abdominal injection of Novocain. ¹⁰¹ Mironchik ¹⁰² combined mechanical and thermal stimulation of the gastric mucosa in dogs by changing the temperature of the balloon; a temperature of 50° C. increased and a temperature of 3° C. decreased the blood pressure. Similarly, cold food (2 to 6° C.) decreased the blood pressure for from one to two hours, followed by an increase, while hot food (48 to 55° C.) produced an initial increase lasting up to three hours, followed by a drop below the initial level. The results are of interest for the standardization of routine measurements of blood pressure, and also for the management of patients: large, very hot or cold meals should be avoided.

Popova ¹⁰⁸ examined the effect of breathing various CO₂ mixtures on the reflex increase of blood pressure produced by mechanical stimulation of the stomach or urinary bladder in normotensive cats. An initial increase was followed by a secondary depression, which could be eliminated by O₂ breathing. The nervous pathways and mechanisms involved in the blood pressure increase upon chemical intestinal stimulation (CO₂, nicotine) and mechanical stimulation

of the urinary bladder were studied by Chernigovskii. 104

The pressor response to mechanical stimulation of intestinal loops or the urinary bladder was more pronounced in rabbits with deafferentiation hypertension 105 than in normotensive animals. An increase of the blood pressure

(up to 30/10 mm.) after infusion of from 50 to 600 c.c. of water into the urinary bladder was found in the majority of 48 subjects; it lasted for from one to 13 minutes and subsided without emptying of the urinary bladder.106 It seemed to be somewhat more pronounced in hypertensive and hyperreactive patients. The pressor response to stimulation of the urinary bladder was abolished in two patients by spinal anesthesia, 106 but could be elicited in cats during urethane anesthesia.107 Palgova 108 studied the pressor effect of urinary bladder stimulation in dogs aged from one day to three months. A reaction to mechanical stimulation appeared after the fifth day, and to chemical stimulation after the fourth day.

The demonstration of pressor responses from the urinary bladder is important for the routine measurement of blood pressure; emptying the urinary bladder would eliminate one of the numerous factors responsible for blood pressure fluctuations.

In most reflex responses, adaptation to stimulation takes place, i.e., the blood pressure returns to the initial level in the presence of continued stimulation. Adaptation occurred within five to 20 minutes of breathing NH, mixtures, and within three to 20 minutes of continued stimulation of the tibialis nerve in rab-Adaptation to urinary bladder stimulation was mentioned before. 106

The pathways of the pressor response to gastric mechanical stimulation were studied by Durmishian. 110 Blood pressure reactions to mechanical stimulation of the jugular, portal and femoral veins and vena cava were investigated by Vasilenko 111 in cats, and of the spleen by variation of the perfusion pressure in dogs by Palgova.112

The depressor effect of increased intrapulmonary pressure (inflation to 110 mm. H₂O) was significantly more pronounced in rabbits with renal and deafferentiation hypertension than in normal animals.113

Injection of low concentrations of acetylcholine, nicotine or NaCN into the femoral bone marrow increased the blood pressure in dogs on the average by 20 mm., while injection of the same amount of 0.9% NaCl was without effect. Injection of acetylcholine or nicotine into lymph nodes by means of fine canules also produced a pronounced increase of blood pressure, while 1% Novocain produced an appreciable fall.¹¹⁴ It was suggested that pressor impulses may originate in the lymph nodes.

In their work on visceral receptors, the Russian authors discovered a number

of potential sources of pressor responses.

It is of interest that the increase of blood pressure on breathing of irritating substances, such as NH₈, was more pronounced in experimental myocarditis produced in rabbits by intravenous caffeine injection,115 because this finding indicates that the condition of the heart may affect pressor responses.

3. Chemical and humoral stimuli. In dogs with experimental renal hypertension, the reaction of the blood pressure to meal intake, adrenalin and nitro-

glycerin was increased and prolonged.116

The pressor response produced by stimulation of the sciatic nerve or skin in dogs and cats consists of an early phase of from 20 to 30 minutes, and a delayed elevation appearing about two hours after stimulation and persisting for six hours or more. After removal of the pituitary gland, or after preliminary adrenal denervation (seven to 30 days before stimulation), the response is limited to the first phase. Two phases of blood pressure elevation were also observed after

intravenous adrenalin injection.¹¹⁷ The increase of blood pressure in hypoxia, produced by closure of the trachea, was more pronounced in rabbits with renal hypertension (²¹, p. 51).

In monkeys with neurogenic hypertension, nitroglycerin or pilocarpine produced an increase of the blood pressure instead of the normal decrease, and the

cold pressor effect was exaggerated.118

4. Diagnostic applications. In the initial, "neurogenic" phase of essential hypertension, a variety of external and internal ("interoceptive") stimuli may elicit exaggerated transient increases of the blood pressure. Sound stimuli tend to increase blood pressure in patients with arterial hypertension, while normal persons are not affected. The cold pressor test is widely used. In hypertensive patients, local heat application tends to produce an increase of the blood pressure instead of the normal decrease (Kupshakova 16, 175). The paradoxical response was later confirmed in plethysmographic records of forearm or hand circulation (see section IV, 5).

Miasnikov (16, p. 173) favors as a diagnostic test the drop of blood pressure after nitroglycerin or amyl nitrite, which is much more pronounced in patients in the early stages of hypertension than in normal subjects. In later phases of

the disease the reaction to nitroglycerin is decreased.

Natanson ¹²⁰ found the cold pressor test to be the best diagnostic procedure in hypertensive patients with cardiac involvement, the sodium amytal test (decrease of blood pressure) in hypertensive patients with cerebral or renal involvement; in the latter, the orthostatic increase of blood pressure was also diagnostically valuable. In general, the higher the blood pressure, the smaller were the pressor effects and the greater the depressor effects. The increase of blood pressure in breathing high CO₂ mixtures (Tolubeeva ²¹, p. 73) or during breathholding was exaggerated in hypertensive patients, particularly in patients with cardiac or respiratory insufficiency, ¹²¹ and this procedure was suggested as a diagnostic test. Lang favors the orthostatic response (¹, p. 100) or the response to breathing CO₂ (¹, p. 98). Martianova ¹²² reported that in patients with malignant hypertension the pressor response to a variety of stimuli (verbal, cold application, etc.) was much more pronounced than in patients with relatively benign essential hypertension.

Blood pressure reflexes are important not only as diagnostic tests but also for standardization of clinical routine measurements of blood pressure. This had already been mentioned in regard to the filling of the urinary bladder and

the effect of meals.

Application of the rubber cuff itself was found to change the blood pressure measured in the contralateral arm, producing an initial slight decrease, followed, after from eight to 10 minutes of compression, by an average mean increase of 18 mm.¹²⁸ The pressor response produced by breathholding paralleled the drop of arterial O₂ saturation but persisted for some time after resumption of breathing.¹²⁸ The observation that a change from nose to mouth breathing frequently decreased the blood pressure is also of interest for the standardization of routine blood pressure measurement.

5. Unconditioned and conditioned peripheral vascular reactions (volume plethysmography). Mechanical recording of volume changes of peripheral circulation in response to various conditioned stimuli, in arterial hypertension as well as in other diseases, is widely used in the U.S.S.R. The procedures are

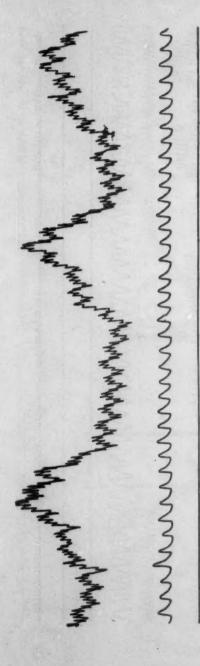
fairly well standardized. A plethysmogram is recorded from forearm, hand or finger, usually by means of mechanic transmission. The resting fluctuations of the plethysmogram, and the time needed to establish a more or less constant base line, were found to be valuable criteria. Figure 4 (taken from Silvestrov, 124) shows exaggerated slow fluctuations (first line), which do not depend upon respiratory cycles (second line). Figure 5 shows normal amplitude of fluctuations, and figure 6 a nearly rigid base line. Exaggerated fluctuations such as shown in figure 4 are typical for early essential hypertension, suggesting a lack of stability of peripheral vascular regulations. In later phases of the disease, hyporeactivity develops and results in subnormal fluctuations (figure 6), suggesting impairment of peripheral regulation. Identical results were obtained by Orlova, 125 Rybkin and Segal, 126 Klepitsova, 127 Alexandrova 128 and Kononiachenko. 129, 180

After the basal plethysmogram has been taken, a stimulus producing a vascular reflex is applied, usually immersion of the contralateral arm into cold (0° to 5° C.) water or warm (about 45° C.) water, normally producing a prompt reflex constriction or dilatation, respectively. The cold or heat application (unconditioned stimulus) is then repeated, preceded by an acoustic or optic signal (conditioned stimulus). After a certain number of repeats (about 10 to 20), the conditioned signals alone produce a reaction which is identical with or similar to the unconditioned response. A certain number of further repeats is needed to stabilize the conditioned reflex. Subsequently, differential inhibition is developed between a positive and a negative signal (for instance, between sounds of different pitch), and often the conditioned sensory stimuli are substituted by verbal signals (Pavlov's "second signal system"). Finally, the speed of extinction is measured (number of repeats without reinforcement until disappearance of the conditioned response). Figure 7 (Ianushkevichus, 181) illustrates the criteria for evaluation of the conditioned responses (in this case, vasoconstriction to cold on exposure to yellow light: latent period "6," amplitude "7" and duration "8," as related to duration of conditioned "2" and unconditioned "3" stimulus. Differential inhibition is shown in "10": no response to red light. The latent period, duration and amplitude of unconditioned reflexes are evaluated in the same way (not shown in figure 7).

In essential hypertension the unconditioned vasoconstriction on cold application is exaggerated. Figure 8, taken from Miasnikov (16, p. 46), shows the typical response of a normal subject and a patient. In contrast, the vasodilatation to heat application is diminished in patients, and vasoconstriction instead of the normal vasodilatation often occurs, as illustrated in figure 9 (16, p. 47). In later phases of hypertension the responses become weaker, and fatigue develops fast on repetition. 125, 126, 127 These results in patients with essential hypertension reveal an impairment in the adjustment to environmental temperature. It appears that an even, moderate environmental temperature would be desirable

for patients with arterial hypertension.

The differences between patients and healthy subjects were found to be much more striking in regard to the conditioned than to the unconditioned responses. In the early phase of arterial hypertension the formation of conditioned reflexes to cold application was accelerated: instead of the 10 to 20 repeats needed in normal people, the conditioned reflexes were obtained after from four to six repeats. The latent period ("6" in figure 7) was shortened, and the amplitude



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ch es. es in ix Fro. 4. Exaggerated phasic fluctuations (Silvestrov 124). Top line, basal forearm plethysmogram; second line, respiration; third and fourth lines, for stimulus signals (not used in this tracing); fifth line, time signal.

Fro. 5. Average fluctuations of basal plethysmogram (Silvestrov 124). Same arrangement of lines as in figure 4.

6. Stable plethysmogram (Silvestrov 124). Upper line, plethysmogram; lower line, time.

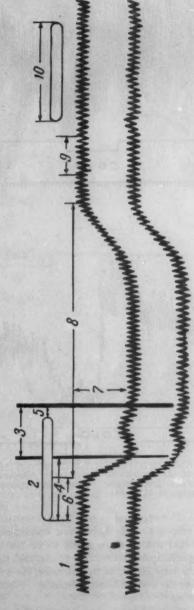
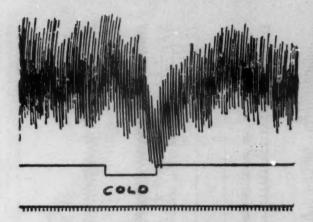


Fig. 7. Criteria for evaluation of conditioned vascular reflexes. Upper tracing, volume plethysmogram of left middle finwer tracing, right middle finger. 1—base line; 2—conditional stimulus: yellow light, exposure time 30"; 3—reinforcement with unconditioned stimulus—local cold application (4 to 6° C.) for 20"; 4—isolated action of conditioned stimulus; 5—isolated action of conditioned stimulus; 5—isolated action of response; 3—duration of response; 9—return to initial base line; 10—differential inhibition (no response to red light). Reproduced from lanushkevichus. 31



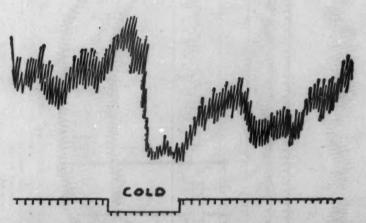


Fig. 8. Reflex vasoconstriction of forearm in response to immersion of contralateral arm into cold water. Upper tracing, normal subject; lower tracing, hypertensive patient. (Miasnikov, 16 figures 10, 11, p. 46).

was increased. The response to heat application was often paradoxic, like the unconditioned response. Of the various conditioned signals (optic, acoustic, verbal), the verbal stimuli were found to be the most powerful. Figure 10 shows an exaggerated vasoconstriction to a verbal signal announcing cold application.¹²² In the later phases of hypertension the conditioned response becomes hyporeactive, like the unconditioned response. Similar observations were made by various authors.¹²³

Disturbance of conditioned vascular reflexes in essential hypertension is of interest for two reasons: it shows impairment in the environmental adaptation

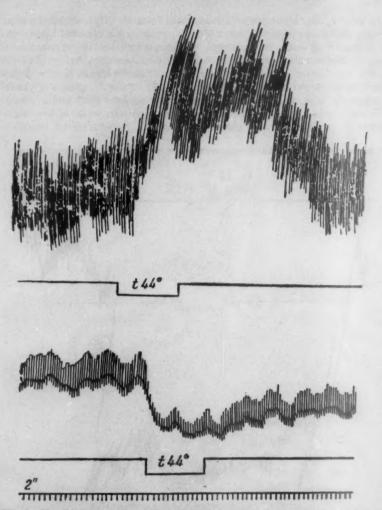


Fig. 9. Vasodilation in response to immersion of contralateral arm into warm water of a normal subject (upper tracing) and vasoconstriction in a hypertensive patient (lower tracing) (Miasnikov, 16 figures 12, 13, p. 47).

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(similar to the unconditioned responses), and it shows also, with a semi-quantitative objective method, an early involvement of the cerebral cortex. The fact that this involvement changes from a hyperreactive to a hyporeactive response tends to support the concept of primary C.N.S. involvement, although it is not conclusive. Disturbance of conditioned and unconditioned reflexes is not specific for essential hypertension, nor does it determine the development of a specific form of vascular pathology. The changes in vascular regulation are part of a more general disturbance of autonomic complex reactions. 184

In this regard, Mansurov's ¹⁸⁵ study is of interest. He compared vascular reflexes, plethysmographically recorded, in patients with essential hypertension and in those with active rheumatism. In contrast to essential hypertension, the unconditioned vascular reflexes in rheumatic patients are already inert in an early phase of the disease, and the formation of conditioned reflexes is slow or abolished. Hyporeactive vascular reflexes occur only in the late phases of essential hypertension. On the other hand, in rheumatic patients meal intake produces the normal, pronounced increase of the pulse amplitude, while in hypertensive patients the plethysmogram remains unchanged. Disturbances of conditioned

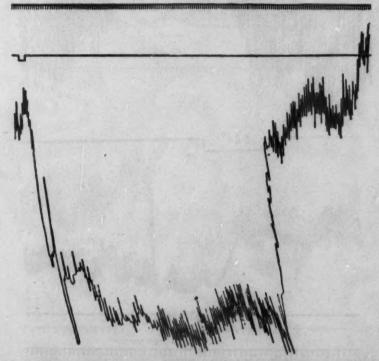


Fig. 10. Exaggerated vasoconstriction (lower tracing) on verbal signal (middle line) in a hypertensive patient. Upper line: time in seconds (Zaslavskaia 182).

vascular reflexes have been observed in various diseases, but there still might be differences in the type of changes, as is suggested by Mansurov's results. It should be noted that hyporeactive responses may occur not only in disease but also in normal subjects after physical fatigue, sleep deprivation (restored by sleep), or in hunger (restored by meals).¹⁸⁶ The vasoconstriction concomitant with mental work (calculations) and with breathholding may be of potential diagnostic interest. Both reactions are increased in patients with essential hypertension, as illustrated in figures 11 and 12 (reproduced from Miasnikov ¹⁶, figures 14-16).

In addition to plethysmographic recordings, changes in arterial pulse contours have been studied. Bragina 186 recorded simultaneously, with piezocrystal pick-up, the pulse from the temporal and radial arteries in 20 normotensive subjects and in 88 patients with essential hypertension. In the normal control group, mental work (calculations) produced a slight increase of the pulse amplitude in the temporal artery and/or a slight decrease in the radial artery; breathholding as a rule produced no significant change, and local cold application produced a

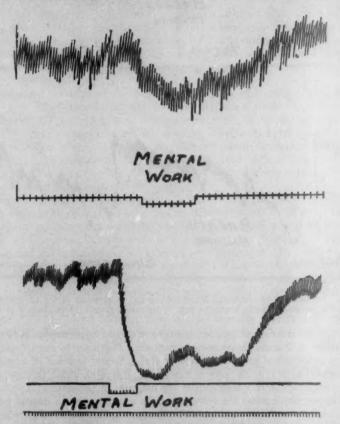


Fig. 11. Vasoconstriction in mental work; upper tracing, normal subject; lower tracing, hypertensive patient (Miasnikov, 16 p. 48).

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decrease of the amplitude in both arteries. In 20 out of 22 patients in the first stage of essential hypertension, the increase of the pulse amplitude in the temporal artery during mental work was much more pronounced (up to four times the original amplitude), while usually the amplitude of the radial artery pulse decreased. The changes of the amplitudes in breathholding were also exaggerated in patients in early essential hypertension, but to a lesser extent than was the reaction to mental work. The reaction to cold application showed the least

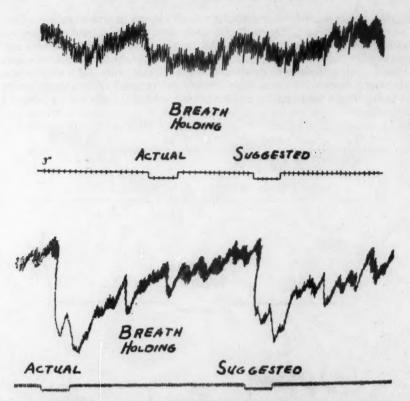


Fig. 12. Vasoconstriction in actual breathholding and in response to the command; upper tracing, normal subject; lower tracing, hypertensive patient (Miasnikov, 16 p. 48).

significant differentiation between normotensive and hypertensive patients. In later phases of essential hypertension, paradoxic responses to mental work were common (increase of pulse amplitude in both arteries, decrease of amplitude in the temporal artery). In spite of clinical improvement under therapy, the abnormal responses were maintained in the majority of patients.

In hypertensive crises the response of the arterial pulse to mental work and breathholding was always abnormal. Frequently the pulse amplitude in the temporal artery decreased instead of slightly increasing. The difference between the changes in the temporal and in the radial arteries is of interest in regard to cerebral involvement, and this relatively simple method appears to have promise for clinical application.

Gelfer ¹⁸⁷ used changes in skin temperature as an index for peripheral circulation in response to local cold and heat application in 48 patients with essential hypertension. The change of the temperature measured at the right wrist and right and left shoulder in response to local heat or cold application to the left arm was within normal limits in only 15 hypertensive patients. A pronounced asymmetry between right and left was noted in others (up to 3.2° C.).

V. STATE OF THE CARDIOVASCULAR SYSTEM IN ESSENTIAL HYPERTENSION

Examination of the functional state of the cardiovascular system (electrocardiogram, heart sounds, cardiac decompensation, etc.) in patients with essential hypertension is a part of clinical routine and need not be specifically reviewed. In this section we have considered primarily methods that have not yet become routine. The selection of material for this section was perhaps the most difficult one, and its arbitrary character is obvious.

1. Blood pressure. Korotkoff's sounds are used as standard method for arterial blood pressure determination, as elsewhere. Oleinik records Korotkoff's sounds from a microphone placed on the brachial artery, together with the pressure in the cuff. While the technic itself is not new, the rugged and compact device designed for use of the practitioner would make its wider application

feasible.

A thorough analysis of the hemodynamic basis of Korotkoff's sounds, together with other most commonly used hemodynamic methods, was made by Savitskii. Of particular interest is his method of "tach-oscillography." The speed of volume changes of the brachial artery is recorded by means of a differential manometer connected with the pressure cuff, simultaneously with the radial artery pulse. In addition to diastolic, mean and systolic pressures, this method permits separation of the kinetic and static pressure components. This was verified in model and animal experiments.

The method was used together with measurements of the arterial pulse wave velocity (optical recording) and the cardiac minute and stroke volume (acetylene method) in normotensive subjects and in hypertensive patients. Savitskii's systolic "end pressure" corresponds to the conventional systolic (or maximal) pressure, and is the sum of the static and kinetic pressures. In healthy subjects the static pressure is about 90 to 100 mm., and the kinetic pressure about 10 to 20 mm. In hypertensive patients the kinetic pressure increases up to 50 to 70 mm., i.e., relatively more than the "end pressure." Table 2 shows typical results obtained in hypertensive patients.

Cases Ch and A have identical minute volume and a moderate difference in the diastolic and maximal systolic pressure, while the relative differences in

Table 2

Blood Pressure in Patients with Arterial Hypertension Determined by Savitskii's Method (Excerpt from Tables 8 and 9, Savitskii¹⁸⁹)

	Blood Pressure				Pulse	Cardiac	
Patients	Diastolic	Maximal Systolic	Static	Kinetic	Wave Velocity M./sec.	Stroke Volume c.c.	Minute Volume c.c.
P	90	225	165	60	9.5	112	6800
Ch	120	230	208	22	10.6	30	2100
L	130	220	190	30	13.3	40	2800
A*	145	250	200	50	24.0	30	2100
V (Admission)	98	210	160	50	15.3	67	4470
V (2 weeks in hospital)	133	240	205	35	9.2	62	4140
M (Admission)	73	172	130	42	11.3	100	6790
M (2 weeks in hospital)	65	155	140	15	15.0	98	6340

^{*} Pre-uremic condition.

kinetic pressure component and pulse wave velocity are great. A parallelism between pulse wave velocity and kinetic pressure, however, is not always present; case P has a high kinetic pressure, a relatively low pulse wave velocity, and a high cardiac stroke and minute volume. In case V, diastolic and systolic end pressures increased during a stay of two weeks in the hospital, minute and stroke volume did not change essentially, while aortic pulse wave velocity and kinetic pressure decreased. Case M has a low diastolic pressure, and the moderate hypertension is therefore primarily of cardiac origin, associated with increased stroke and minute volume. After a stay of two weeks in the hospital there occurred a slight increase of the static pressure component and a drastic drop of the kinetic pressure component. The correlation between the various indices seems not to have been examined systematically, but it appears that measurement of the static and kinetic component gives useful information which cannot be obtained from other measurements. As to the clinical value, in Savitskii's experience an increase of the kinetic pressure component usually parallels a deterioration in the clinical condition, and often precedes retinal or cerebral hemorrhage. While it is too early to attempt to make conclusive clinical evaluation. the results would seem to encourage a wider application of this comparatively simple method.

The variability of the blood pressure is considered to be a typical feature in the initial ("neurogenic") phase of essential hypertension. In studying this problem, Ivanov 140 used 10 measurements made at three-minute intervals. The variability was, in fact, significantly increased in the early phase and decreased

in the late phase of hypertension.

The question of regional cerebral hypertension was studied in 95 patients with arterial hypertension and cardiovascular cerebral accidents. In the majority (70%), the blood pressure in the temporal artery was significantly higher on the side of the cerebral lesion, i.e., unilateral neurologic lesions were often asso-

ciated with significant right-left differences in the blood pressure.

The problem of regional hypertension was approached by Volkova, 140 using Baillart's ophthalmodynamometry. The method consists in the ophthalmoscopic observation of pulsation in the retinal vessels upon increasing external pressure against the side of the eyeball. Appearance of pulsations indicates the diastolic pressure and disappearance of the systolic pressure in the central retinal artery. The pressure in the retinal artery (RA) is normally closely related to that in the brachial artery (BA), and their ratio (RA: BA) is used as a criterion of regional hypertension in the retinal artery. Out of 965 patients with arterial hypertension, the ratio was increased in 43 patients. While this number is quite small, the pressure ratio was found to be of clinical importance. A regional pressure increase in the retinal artery often preceded a general blood pressure increase, and a relatively high retinal artery pressure was found to be prognostically unfavorable.

2. Pulse wave velocity. The pulse wave velocity has frequently been studied in arterial hypertension inside and outside the U.S.S.R., since it is related to the elastic properties and tension of the arterial wall. It increases with the blood pressure, and is therefore significantly higher in hypertensive patients than in normotensive subjects. Since the main object of this method is the analysis of the elastic properties of the arterial wall, the dependence upon the blood pressure is a disadvantage. The correlation between blood pressure and pulse wave velocity

is too low for prediction in normotensive as well as in hypertensive individuals, 142b

in spite of significant group differences.

Nikitin's ¹⁴³ approach, which eliminates the absolute blood pressure level as reference point, is therefore of considerable interest. He determined the normal limits of the ratio of pulse wave velocity in muscular arteries ("Cm," measured between subclavian and radial artery by means of Broemser and Ranke's method) to that in elastic arteries ("Ce," measured between carotid and femoral arteries, representing mainly the aorta). The range, determined in 137 normal subjects, extends from 1.11 to 1.30, with a mean of 1.21. The ratio Cm: Ce was extremely variable in patients in early essential hypertension (range from 1.0 to 1.8), but in general it was elevated. However, in the second and third stages of hypertension (using Lang's classification), the ratio is significantly decreased (range: 1.08 to 0.6, and 1.1 to 0.5, respectively), because the increase of pulse wave velocity in the aorta (Ce) exceeds that in the brachial-radial artery. This is believed to be due to a decrease of muscle tone in the muscular arteries, as a functional compensation. Nitroglycerin, in one typical experiment, decreased the ratio from 0.9 to 0.68.

This method was used also in combination with the cold pressor test. In normotensive subjects, local cold application produced a slight increase of Ce (about 0.5 m./sec.), and a somewhat larger increase of Cm (about 1 m./sec.). The effect of cold was highly variable in the first stage of hypertension, but in patients in the second stage the increase of the pulse wave velocity was often pronounced, usually more so in Ce, so that the ratio Cm/Ce declined. In one example, Ce increased from 1.7 to 2.55 m./sec., Cm from 1.5 to 2.0 m./sec., and the Cm/Ce ratio dropped from 0.88 to 0.78. The blood pressure increased from 212/106 to 254/124 mm. of Hg, which is a pronounced change, though still relatively smaller than the change of the pulse wave velocity. However, the over-all correlation between the change of the blood pressure and that of the pulse wave velocity appears to be low. The drop of the Cm/Ce ratio in the cold pressor test, seen in the early stages of hypertension, seems to anticipate a change typical of the more advanced stages.

3. Arterial pulse. Using a piezocrystal pickup, Pushkar 144 recorded on a two-channel electrocardiograph the contour of the pulse in the carotid and femoral arteries in 38 normotensive subjects and 196 patients with arterial hypertension. Together with an acceleration of the pulse wave velocity, it was found that the upstroke and downstroke of the arterial pulse were slower in the hypertensive

patients.

4. Circulation time, venous pressure. The use of these criteria has become clinical routine for evaluation of decompensation in the U.S.S.R., as elsewhere, and need not be reported in detail. Of interest is the use of radioactive sodium, ¹⁴⁵ since this method permits the determination of the pulmonary circulation time as a difference between two peaks recorded with a precordial pick-up, after injection into the cubital vein. The first peak is interpreted as arrival in the right ventricle, the second peak as arrival in the left ventricle. The range of the pulmonary circulation time was from 5 to 7 seconds, with a mean of 6.2 seconds in 20 healthy subjects from 18 to 52 years. It was already prolonged in 30 patients in the first stage of arterial hypertension (mean, 7.1 seconds), and increased progressively with the course of the disease (7.5 seconds in 51 patients in the second stage, 9.2 seconds in 12 patients in the third stage). The general

circulation time was measured from a pick-up in the contralateral arm. Later, Fateeva increased the sample to 300 patients, with the same results. It appears that pulmonary circulation time might be a more sensitive index than is the general circulation time for detection of early decompensation. Bobkova, Rsaev and Solevev 148 found a prolongation of the arm-to-arm circulation time, determined with radioactive sodium, in general in parallel to cardiac decompensation, but in some patients it was prolonged without clinical symptoms of decompensation.

Thorough studies of the venous pressure in 55 patients with essential hypertension were performed by Davidov. The time of measurement was extended to 15 minutes, since single measurements were found to be unreliable because of interference of emotional effects. The time needed for attaining a base line was a valuable index, in addition to the height of the basic level itself. The venous pressure was highly variable, like the arterial blood pressure. The time to reach the base line was prolonged in essential hypertension and shortened under treatment. The venous blood pressure increased with the course of the disease and the development of decompensation. Table 3 gives a condensation of Davidov's results.

Table 3

Average Values of Venous Pressure (mm. H₂O) and Circulation Time (sec.) in Essential Hypertension (Davidov¹⁶⁹)

Stage	Initial	Base Line	Differential	Time to Reach Base Line	Circulation Time, Sec.
I	190	133	57	12 min.	10.7
II	176	144	32	11 min.	17.2
III	190	168	22	9 min.	23.7
IV .	215	212	3	8 min.	32.0

5. Cardiac involvement—x-ray, electrocardiogram. Decrease of the amplitude of ventricular contractions in the x-ray kymogram was found to be a valuable early sign of cardiac involvement in 70 patients with arterial hypertension. Changes in the electrocardiogram occurred considerably later; a shift to the left of the QRS axis preceded the development of frank abnormality. Of interest is the comparatively early right ventricular involvement observed in x-ray kymograms. The finding was corroborated by Ivanitskaia. 151

In contrast to the findings of Bagdarasov et al., 150 Soleva 152 found early changes in the electrocardiogram on comparing 200 patients in the first ("neurogenic") phase with 100 healthy subjects of the same age. These changes were still within the "normal" range, but in the direction of changes which might be produced by developing left ventricular strain. They were present in 57% of the hypertensive group. It is entirely logical that changes within the wide normal limits will precede the development of the typical patterns of left ventricular hypertrophy and strain, and deserve diagnostic attention.

In rabbits with deafferentiation hypertension, sacrificed after from one to four months of hypertension, Raiskina 158 found that decrease of adenosine triphosphate and of phosphocreatine and increase of inorganic phosphate in the heart preceded the development of electrocardiographic changes. It is quite probable that chemical changes in the myocardium are also the earliest mani-

festation in essential hypertension in man, but, unfortunately, are not detectable

during life.

In rabbits with deafferentiation hypertension and with renal hypertension, the greatest electrocardiographic changes (left shift of QRS axis, right shift of T axis) occurred in the second month of hypertension, but sometimes electrocardiographic changes developed after from two to three weeks preceding the development of left ventricular hypertrophy.¹⁵⁴ There was no difference between the two types of experimental hypertension in regard to the electrocardiographic changes. In general, there was a relationship between the increase of the blood pressure and the magnitude of the electrocardiographic changes; however, in the later phases the left ventricular strain pattern became less distinct, due to diffuse myocardial degeneration. Regarding late electrocardiographic changes in patients with the pattern of left ventricular strain, the observations in the U.S.S.R. are not different from those made elsewhere.

It is recognized that essential hypertension is an important factor in the development of coronary atherosclerosis, and the use of stress tests is common for early detection of coronary involvement. In 50% of hypertensive patients with normal resting electrocardiograms and without clinical symptoms of coronary insufficiency, Dibner ¹⁸⁵ found an abnormal response to the exercise and anoxia tests. In dogs with experimental hypertension the anoxia test became abnormal quite early, several months before development of an abnormal resting electrocardiogram or abnormal x-ray changes. ¹⁸⁶, ¹⁸⁷

6. Peripheral blood flow. The development of electrocardiographic abnormalities will depend upon the vascularity of the heart. A histologic study of arteriovenous anastomoses in the heart of normotensive and hypertensive patients by Arkhangelskii 158 is therefore of interest. The incidence of anastomoses increased with age, but essential hypertension was a more important factor.

The blood flow in various organs was studied by Aronova et al. 159 in dogs during acute arterial hypertension produced by electrical stimulation of the hypothalamus and of visceral receptors, by compression of the carotid artery, or by hypoxia. Thermo-electric recording of blood flow was used. The coronary blood flow was increased in all forms of acute hypertension, and the cerebral blood flow increased in all forms except for that elicited by the compression of the carotid artery. This was assumed to be due to cerebral vasoconstriction resulting from the absence of impulses from the carotid sinus, rather than to the mechanical reduction of the blood flow in the carotid artery. The results do not

have immediate application to essential hypertension.

7. Capillaries. In 12 rabbits with deafferentiation hypertension the conjunctival capillaries were photographed by means of a specially constructed capillaroscope. As compared to the capillaries of 12 normal rabbits, the capillaries of the experimental animals were elongated, dilated and more tortuous, the capillary wall was thickened, and in six animals the flow was slower and pulsating. The same authors studied finger capillaries in 65 patients with essential hypertension. In the first stage some abnormal features were already noted in 66% of the patients, such as an increase in the number of capillaries and greater irregularity of their contour. The changes increased in incidence and severity with the progressive course of disease (prolongation, tortuosity and dilatation of the venous part similar to the results obtained in rabbits with experimental hypertension). In 11 patients the clinical condition was improved by sleep therapy,

but the capillary circulation was improved in only six individuals. The results were confirmed by Rusanov, 162 who also found lengthening, tortuosity, and dilatation of the venous and spasm of the arterial segment in 20 hypertensive patients. Adrenalin produced a slowing of the capillary flow in hypertensive patients, in

contrast to healthy subjects.

Capillary permeability was studied by Ratner and Spivak ¹⁶⁸ in 175 patients with essential hypertension, using Landis' method. The permeability was increased, as compared to healthy subjects, in 73, 82 and 87% of patients in the first, second and third stages, respectively, of essential hypertension. In spite of the progression with the clinical course, there was no correlation with the level of blood pressure. In the first stage of hypertension, chloral hydrate depressed the abnormally increased permeability, but in the second and third stages the results were not uniform.

8. Arterial oxygen saturation. In the early stages of essential hypertension the arterial O₂ saturation and oxygen dissociation of hemoglobin curve were normal, but in the third stage there was a shift of the O₂ dissociation curve to the right, with a loss of its S-contour. In the absence of acidosis or change in the CO₂ combining power, this might be a compensation mechanism facilitating the oxygenation of tissues, perhaps due to changes in the globulin component of hemoglobin produced by renin.¹⁶⁴

9. Hypertensive headaches. In general, clinical observations are not included in this review because they parallel to a large extent those made outside the U.S.S.R. However, the research on hypertensive headaches deserves mention because they are one of the outstanding clinical symptoms in essential hyper-

tension, related to intracranial circulation.

Kedrov 165 presents a thorough discussion of the mechanism of hypertensive headaches, based on his extensive experimental work with Naumenko 166 on intracranial circulation by means of impedance plethysmography. They found a direct mechanical transmission of arterial pulsation to the veins, producing pulsating flow in the cerebral veins, with arterial configuration of the pulse contour but with smaller pulse magnitude than in the arteries because of the greater volume capacity of the venous bed. Rejecting the hypothesis of regional cerebral hypertension, Kedrov suggests that, due to the greater amplitude of pulsations with the increased pulse pressure in arterial hypertension, the venous pulsations are also increased and stimulate sensory receptors in the large cerebral veins and venous sinuses, particularly in the confluens sinuum. This agrees with the occipital location, the pulsating type of headaches, and with occurrence of headaches in the morning when the blood pressure rapidly increases during the transition from rest to activity. The increase of venous pulsations with increase of arterial blood pressure was demonstrated in acute animal experiments. Romodanova and Gorbach 167 found increased pulsation of the spinal fluid pressure in 200 hypertensive patients during the time of headaches, whereas there was no correlation between the changes of the absolute pressure of the spinal fluid and headaches. These findings agree well with Kedrov's hypothesis. On the other hand, Urinson 108 found no increase of spinal fluid pulsations in essential hypertension. He did not study the effect of headaches on these pulsations.

Increase of the tone of the cerebral arteries is suggested as a compensatory mechanism. The exacerbation of headaches after nitroglycerin is explained by a decrease of the tone in the cerebral arteries, with resulting augmentation of

arterial (and venous) pulsations. The failure of drugs to increase the tone of cerebral arteries, together with a decrease of the general arterial blood pressure, explains the difficulty of drug treatment of hypertensive headaches. The author favors oxygen treatment, which in animal experiments decreased the amplitude of intracranial pulsations.

In passing, it may be noted that there is frequently a disturbance of respiratory movements in essential hypertension, particularly in patients with cerebral

symptoms or with coronary insufficiency. 189

VI. KIDNEY AND HUMORAL FACTORS

The majority of Russian authors consider renal involvement to be a secondary and, according to Lang's classification, a rather late development. Zakharev-

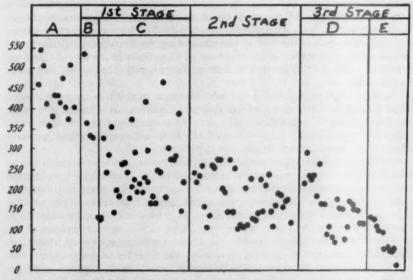


Fig. 13. Renal blood flow, in c.c./min., in a normal control group A and in various stages of hypertension, according to Lang's classification (Ratner, 272 figure 3).

skaia ¹⁷⁰ found normal kidneys in an appreciable number of autopsied patients with essential juvenile hypertension. Similar results were obtained outside the U.S.S.R. On the other hand, Ivanov ¹⁷¹ and N. A. Ratner ^{172, 173} found a decrease of renal blood flow, determined with phenol red and Diodrast, in the early phase of hypertension (transitional stage), progressing with the course of the disease (figure 13). Some negative association between the level of diastolic blood pressure and decreased renal blood flow was noted in the whole group of hypertensive patients. In individual patients in the first stage of hypertension the renal blood flow was diminished only on days with elevated blood pressure; on days with lower blood pressure the renal blood flow approached normal values. This was considered to be evidence that even the early renal ischemia is a secondary development, resulting from spasm in the renal arterioles, present together

with arterial spasm in other regions. M. Ia. Ratner ¹⁷⁴ confirmed the decrease of renal blood flow already present in the early phase of essential hypertension, and the further progressive drop with the course of the disease. The concept of secondary renal involvement was strengthened by the increase of renal blood flow in hypertensive patients after barbiturates and chloral hydrate. ¹⁷⁵ The increase (on the average about 50% and in some patients up to normal values) was most pronounced in the first and second stages, and declined in the third stage with progressive development of renal arteriosclerosis. In contrast, M. Ia. Ratner ¹⁷⁴ found a decrease of renal blood flow after barbiturates in hypertensive patients. Samoilova ¹⁷⁶ observed in three normal dogs and in three dogs with renal hypertension a decrease of renal blood flow and blood pressure after barbiturates and chloral hydrate. The drop of the renal blood flow was more pronounced than was that of the blood pressure, and the time course of the changes was different.

Sleep therapy, in the course of which sedative drugs (barbiturates, chloral hydrate, bromide) were administered over a period of from two to three weeks, increased the renal blood flow in patients during the first and particularly the second stage of hypertension (in seven out of 11 patients in the second stage, up to normal values). The effect of sedative drugs is still controversial and needs further study.

Vasodilating drugs (such as decholin or nicotinic acid) increased the renal blood flow up to 100% in the earlier stages of hypertension, whereas later, with the development of renal arteriosclerosis, these drugs had no effect. The response to vasodilating drugs is considered to be a valuable method for early detection of renal arteriosclerosis.

In 20 rabbits with experimental renal hypertension (the renal arteries having been compressed to one third of the original diameter), Vyshatina ¹⁷⁸ studied the time course of changes of renal blood flow (phenol red) and glomerular filtration (inulin). The peak of hypertension occurred within from three to five months. After a transient decrease of the renal blood flow for from one to two months, it increased to the original level within from three to five months, parallel to the development of arterial hypertension. A permanent decrease of renal blood flow, filtration rate and reabsorption occurred only after from six to seven months.

The failure of denervation of the kidney to prevent the development of hypertension in experimental renal ischemia ¹⁷⁹ is not considered to be an objection to the concept of a central nervous basis of early renal ischemia (¹⁶, p. 97). Conditioned diuretic reflexes in dogs had been maintained after kidney denervation, although they were slower.^{180, 181, 16} The hypophysis seems to be involved in the humoral mediation of conditioned diuretic reflexes. In dogs with established conditioned diuretic reflexes and unilateral kidney denervation, removal of the hypophysis abolished the conditioned reflexes on the denervated but not on the intact kidney, suggesting a dual pathway of mediation.¹⁸¹ Hyperactivity of the hypophysis in essential hypertension was suggested by Zavelova,¹⁸² who found that injection of blood from hypertensive patients increased the number of erythrocytes and reticulocytes to a greater extent than did blood from normal subjects.

While denervation of the kidneys does not abolish experimental renal ischemia, it does abolish deafferentiation hypertension. 188

The volume of research on renin is small as compared with the literature out-

side the U.S.S.R. The Russian authors regard renin as an auxiliary factor in the development of hypertension. Serebrovskaia et al. 184 studied the renin content of the blood in 53 patients with essential hypertension, in normal subjects, and in patients with cardiac, pulmonary and renal diseases. Renin was found only in patients with essential hypertension. It was absent in the first stage, and present in eight of 16 patients in the second stage, and in 7 of 26 patients in the third stage. Although positive findings are more frequent in this series than in those of some Western authors, the results speak against functional significance of renin for pathogenesis or maintenance of hypertension, corroborating

the general consensus.

In hypertension produced by deafferentiation of the carotid sinus, the renin content in the kidneys is increased within one and one-half months but disappears within three weeks after kidney denervation. 188 Ratner and Eisengardt 185 studied the effect of renal denervation on renal blood flow, glomerular filtration, and content of renin in the kidney in normotensive rabbits and in rabbits with deafferentiation hypertension. Renin increased in the first month of hypertension (on the average about two and one-half times), and remained at that level through the period of observation (three months). There was no essential change of renal blood flow and glomerular filtration. In the first days after denervation there was a slight drop of the renin content, and a more pronounced drop of glomerular filtration and renal blood flow, which was interpreted as an effect of stimulation during the operation. In the second and third weeks after denervation, renin continued to drop significantly below the initial level, approaching zero, while glomerular filtration and renal blood flow returned to the initial level. The reaction of normotensive and hypertensive animals was similar in direction, but the drop of the renin content was more pronounced in the hypertensive animals because of its increased initial level. Chernigovskii 183 also found an increase of renin within one and one-half months of deafferentiation hypertension, and disappearance within three weeks after kidney denervation. These results show that production of renin in deafferentiation hypertension is not due to renal ischemia.

Regarding the mechanism of action of renin, Chernigovskii 183 found that injection of renin into the kidney isolated from systemic circulation but with intact nerve supply produced a prolonged increase of the blood pressure, which was prevented by Novocain injection preceding the renin injection. At least in part, the renin effect seems to be mediated through vascular reflexes. The effect was diminished in repeated injections.

Involvement of a vascular reflex is supported by a significant pressor effect of renin injection into an isolated in situ segment of the jugular vein. 186 This effect could also be abolished by Novocain, as in Chernigovskii's experiments on the

isolated in situ kidney (see figure 14).

Kovaleva 187 confirmed the specificity of antirenin to the particular renin preparation used.

In view of the extensive literature on unidentified pressor substances in blood and spinal fluid, only a few representative Russian studies will be quoted. Spinal fluid from hypertensive patients had a more consistent, more pronounced and more prolonged pressor effect than did that from normotensive subjects. Last Vasoconstriction of the ear vessels in rabbits was produced by spinal fluid from hypertensive patients but not by that from normal subjects.

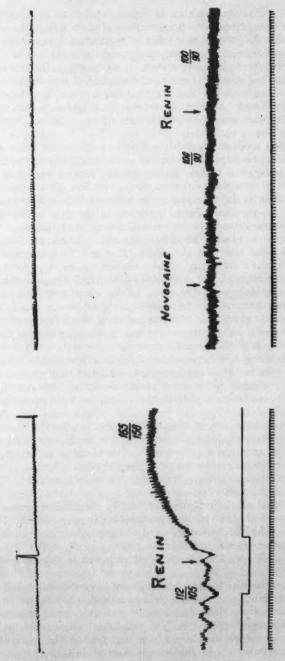


Fig. 14. Injection of renin into isolated in situ segment of jugular vein produces increase of blood pressure (left), which is prevented by 1% Novocain injection (right) preceding the renin injection. (From S. V. Andreev et al. 180)

On the other hand, Rumiantseva-Russkikh 180 found no correlation between angiospastic substances in the blood of 100 hypertensive patients and the level of blood pressure, and not only pressor but also depressor substances were increased. Keiser 180 found no difference in the effect of blood plasma from hypertensive patients and normal subjects on the arterial blood pressure of cats and dogs.

In neurogenic hypertension produced in 11 dogs by application of kaolin powder in the cisterna magna, pressor substances appeared in the blood after from 15 to 20 days, whereas in nine rabbits with deafferentiation hypertension

pressor substances were absent.191

After unilateral temporary occlusion of renal blood supply, Pituitrin-like as well as renin-like pressor substances were secreted by both kidneys of dogs. Pituitrin-like urinary extracts were also found to acquire a considerable oxytocic activity preceding the development of high blood pressure. In one of the dogs the rise in oxytocic activity preceded liberation of a pressor renin-like factor.¹⁹²

Blood serum of patients in the first stage of essential hypertension had an inotropic effect on the frog heart, which decreased in the second stage. Blood serum of rabbits with renal hypertension also exerted an inotropic effect on the isolated frog heart. The pupillary dilatation on local epinephrine application to the eye was increased in the hypertensive animals. The peak of both the inotropic effect and the pupillary dilatation occurred in the third month of hypertension. The author concluded that sympathomimetic substances are increased

in hypertension.

Buguslavskaia 40 found increased epinephrine in essential as well as in secondary renal hypertension, which was not confirmed by Spivak.41 Zhislin and Smazhnova 42 noted both an increase and a decrease of epinephrine in hypertensive crises. Excretion of urosympathin was decreased initially in hypertensive crises, followed by a pronounced increase. In an investigation of 50 patients, epinephrine was within normal limits through all three stages of essential hypertension, while norepinephrine increased with the course of disease. In the first stage, norepinephrine was within normal limits; in the third stage, it was increased in about 50% of the determinations (16, pp. 72 and 73). Unfortunately, the results are given in terms of determinations rather than in number of patients, with varying number of repeats in individual patients. The scatter of the values is quite large. In chronic nephritis, epinephrine and norepinephrine were within normal limits (16, p. 73).

On the whole, the subject of the role of adrenergic substances in essential hypertension is controversial in the U.S.S.R. In the Western literature there is no definite evidence of increased epinephrine in the blood of patients with

essential hypertension (Raab 193, p. 279).

Sribner, 106 Kakushkina and Mentova 107 and Ilevich 108 found in essential hypertension an increase of cholinesterase activity. In six dogs with neurogenic hypertension produced by conflicting conditioned reflexes, the fluctuations of

blood pressure and cholinesterase activity coincided closely.

Ratner and Ospenskova ¹⁹⁸ studied hypertensive crises in essential hypertension in the expectation that the changes associated with the transient increase of blood pressure to a very high level would have some bearing on the theory of pathogenesis. Two types of crises are differentiated: (1) the acute type, lasting from several minutes to several hours and occurring mostly in the first

and second stages of hypertension and (2) a more prolonged type (four to five days), with pronounced cerebral symptoms. Leukocytosis occurred in both types, but more so in the second (prolonged) type. Coagulation time was shortened in 80% of the acute crises and in 94% of the prolonged crises, and this was associated with a pronounced increase of blood cholesterol (up to 180% of the initial concentration).

In summary: While renal and humoral factors are considered to be secondary, their functional significance in the development and maintenance of hypertension is recognized. The detection of renin and the decrease of renal blood flow in the early phase of essential hypertension do not fit Lang's classification.

VII. THERAPY

The Russian literature on the treatment of essential hypertension is extensive. With respect to the use of adrenergic blocking drugs, Serpasil, sympathectomy, etc., and to the treatment of cardiac decompensation and other clinical complications, the experience in the U.S.S.R. is similar to that in other countries and therefore will not be reviewed here. We concentrated on material with some aspects of novelty, or some rather direct relationship to the underlying concept of primary C.N.S. involvement, such as the sleep therapy.

As a matter of sheer curiosity, one might mention Galkin's 199 studies on the effect of venous bloodletting with leeches in hypertensive patients. One leech will withdraw about 45 c.c. blood. Subjective and objective results (arterial and venous blood pressure, circulation time, volume plethysmogram) were favorable in the second and third stages of hypertension. The results were not proportional to the amount of blood drawn.

1. Psychotherapy. Miasnikov (16, p. 310) regards the psychotherapeutic factor as an obligatory component in all forms of medical therapy of essential hypertension. Strong excitations, reaching the cortex in the form of speech (the "second signalization system") and forming an important part of stressful life experiences, are believed to play a dominant role in the pathogenesis of hypertension. Consequently, the Russian investigators would expect ex hypothesi that the application of appropriate measures reducing this type of "stress" would have a beneficial therapeutic effect.

Formal psychotherapy is regarded as a potentially important but not a basic element in the complex therapy of hypertensive disease. However, in selected individuals, a "personal reëducation" may be called for, designed to reduce emotional overreactivity and to strengthen the inhibitory processes (16, p. 308).

2. Sedatives. The immediate effect (i.e., several hours after drug administration) of neurotropic drugs, including bromides and barbiturates, was studied by Ivannikova 200 in 625 electroencephalograms of 125 patients with essential hypertension. The immediate changes in the electroencephalograms were similar to those observed in chronic medication using the same drugs, and may be used for prediction of the therapeutic effect.

The clinical effect of bromide therapy was studied in 70 patients with essential hypertension using the electroencephalographic and psychomotor responses, in addition to clinical observations, as criteria.²⁰¹ The bromide content of blood before treatment was lower in patients (0.2 to 0.5 mg.%) than in a control group of 20 normal subjects (0.5 to 1 mg.%). Daily dosage of 2 gm. sodium bromide

over a period of two weeks increased the bromide content in blood more in the normal than in the hypertensive group. In patients with the "strong" type of nervous system (see Section III-3), clinical improvement occurred when the blood bromide reached 49 to 59 mg.%, in patients with weakened inhibition at 35 to 46 mg.%, and in patients with weakened excitatory processes at 28 to 41 mg.%. In the last group, increase of bromide over 41 mg.% produced deterioration.

3. Sleep therapy. The sleep therapy of essential hypertension appears to be one of the most important recent developments in the U.S.S.R. Perhaps more than any other procedure, it agrees with the Russian concept of primary C.N.S. involvement. Sleep therapy, as such, is not new. Sedatives have been widely used in the treatment of hypertension for a long time, and the beneficial effect of bed-rest is well known. However, sleep therapy in the U.S.S.R. is used more systematically than elsewhere. At the same time, experimental research on the physiologic effects of sleep in normotensive and hypertensive states has been carried out on a large scale. Since primary C.N.S. involvement is assumed in a large number of diseases, sleep therapy is not limited to hypertension. In a 1954 monograph on sleep therapy 202 applications to various diseases were considered. Here the discussion will be limited to selected reports, with emphasis

on experimental data.

Therapy with prolonged sleep was initiated in hypertensive patients by Andreev (16, p. 314), who used 0.5 to 1.0 gm. sodium amytal plus 0.1 to 1.5 gm. chloral hydrate per day, producing daily 18 to 20 hours of sleep over a period of 20 to 25 days. While the therapeutic results were encouraging, in subsequent studies equally good results with fewer side-effects were obtained with reduced dosage and reduced period of administration. Today, most authors use various sedatives in doses calculated to produce from 14 to 16 hours of sleep per day over a period of about two weeks. Among sedative drugs, barbiturates and chloral hydrate are frequently used, mostly in combination and often with the addition of bromides. Shapiro and Alfeev 208 add papaverine to barbiturates and bromides. Miniovich 204 combines sleep therapy with intramuscular injection of magnesium sulfate. Kreimer 205 used hypnotically induced sleep in two sessions daily from six to eight days, in combination with bromides. Lizunova 200 produced conditioned sleep, starting with barbiturates and chloral hydrate, which were replaced after from five to seven days by placeboes. In the majority of patients, placeboes produced sleep of about the same duration as that produced by sedative drugs.

The reports are favorable throughout; in a considerable proportion of patients a fairly immediate clinical improvement (drop of blood pressure, disappearance of headaches, etc.) has been reported, outlasting the period of treatment by many months. There is, however, a considerable variation in the percentage of positive results. In the large material of the Institute of Therapy in Moscow (16, p. 314), sleep therapy was successful in about 50% of patients with early hypertension. There is general agreement that sleep therapy is successful only in the early phases (stages 1 and 2). Furthermore, it was suggested that the individual type of nervous system, using Pavlov's classification, is important. According to Speranskii 201 and Aleksandrova (16, p. 317), only in patients with the equilibrated and inhibitory types was the sleep therapy successful, while in patients of the excitatory type sleep therapy was not successful, and

sometimes was even harmful. In patients with excitatory C.N.S. type, Speranskii recommends phenobarbital, and in patients with inhibitory type, chloral hydrate. ²⁰⁸ In view of the unfamiliarity with Pavlov's classification of nervous system types outside the U.S.S.R., Il'ina's ²⁰⁹ criteria for the selection of patients for sleep therapy based on the electroencephalogram are useful. In patients with asynchronous, irregular alpha rhythm of low amplitude, dissociation between right and left hemispheres, appearance of spikes and only slight depression on exposure to light, sleep therapy was not effective. While the electroencephalogram may be helpful in the selection of hypertensive patients, Zhirmunskaya ²¹⁰ found no parallelism between clinical improvement and electroencephalographic changes under sleep therapy.

The varying results of sleep therapy in different patients may also be due to the effect of sleep on arterial oxygenation and respiration. Stupnitskii ¹⁶⁰ found in some hypertensive patients a greater disturbance during sleep of respiratory mechanics than in conscious condition, while it improved in others. In patients with disturbance of respiratory movements in sleep, the arterial oxygen saturation dropped by 1.5 to 4.5%. These characteristics also may be of im-

portance for selection of patients for sleep therapy.

Selection of patients may perhaps explain the impressive results of Alperin et al.,²¹¹ who found good results in 54 out of 57 patients. The improvement may be maintained for some time. Out of 46 patients observed for up to 28 months, Gelfer ²¹² found a favorable effect in 36 patients, lasting for over four months in 29 patients. Lavskii and Borisova ²¹⁸ reported a duration of improvement of from eight to 10 months in most patients with a positive response to sleep therapy. On the other hand, out of Semenova and Beliaeva's 40 patients, an immediate favorable result was obtained in 34 patients, but it had been maintained in only 23 after six months.²¹⁴

The clinical improvement under sleep therapy has been utilized for the study of changes in various functions. Since the acute effect of sleep is the basis for the effect of prolonged sleep therapy, both acute and chronic effects were quite extensively studied. The less pronounced prolongation of the motor chronaxy during sleep in animals with experimental hypertension was noted earlier (see Section III, 4). Kononiachenko 215 observed disappearance during sleep of the large, spontaneous fluctuations of the volume plethysmogram typical for patients in the early stages of hypertension, an observation that was confirmed by Ivanov.²¹⁶ The base line became more stable, and abnormal vasomotor reactions disappeared. In some patients who did not respond to sleep therapy, vasomotor reactivity was increased. The author suggests that vasomotor reactivity as recorded in plethysmograms may serve as a reliable objective criterion of the success of therapy. Erlikh and Garantova 217 found, together with an improvement of the reaction to local heat application, an increase of the amplitude of the finger plethysmogram after sleep therapy in 20 out of 63 hypertensive patients, particularly when it was small before treatment.

One of the most favorable and best founded reports is that of Smetnev.²¹⁸ Only six out of 118 patients in the first and second stages of hypertension failed to respond with a decrease of the blood pressure to sleep therapy (produced by hypnotic induction). Of 50 patients who responded favorably to sleep therapy, examinaton after an interval of from two to three years revealed that in 15 patients the blood pressure was higher, in 11 unchanged, and in 24 decreased as

compared to the pretreatment value. Subjective improvement lasted up to one year in 35 patients, and up to three years in 14 patients. Before treatment, capillaroscopy revealed in most patients narrowing of the arterial and widening of the venous segment; sleep therapy reversed this pattern in the first but not in the second stage of hypertension. The motor chronaxy, which was shortened before treatment (see Section III, 4), lengthened significantly. The flexor: extensor ratio, which was decreased in most patients, became normal (1:2) in 28 patients. Lengthening of the shortened motor chronaxy under sleep therapy was confirmed by Ivanov. The shortened motor chronaxy under sleep therapy was confirmed by Ivanov. The flexor is patients and Ilchevich and Ilchevich are reported, together with the decrease of blood pressure, improvement of vascular reflexes plethysmographically recorded, prolongation of motor, optic and vestibular chronaxies, and, in some patients, decrease of the increased cholinesterase activity, particularly in the first stage of hypertension; the results of sleep therapy were less pronounced in the second stage.

Beliaeva ²²⁶ followed the physiologic effects of sleep therapy by means of the cold pressor test, skin temperature, orthostatic response of blood pressure and pulse rate, and the response to local heat application. Under sleep therapy these indices improved in the first and, though somewhat less, in the second stages of hypertension. In the series of Alperin et al., ²¹¹ sleep therapy decreased the venous blood pressure and circulation time, when elevated, together with the arterial blood pressure; in some patients a transient improvement of the left ventricular strain pattern occurred, but in other patients the electrocardiogram did not change in spite of clinical improvement. No consistent results were shown by the x-ray kymogram. Renal circulation improved, and in 25 out of 27 patients with leukopenia and relative lymphocytosis the white blood count increased, in the majority to normal values. The increased alpha globulin fractions decreased under sleep therapy, although not to normal values, and there was

The success of the sleep therapy tends to support the concept of central nervous system involvement, not only in the pathogenesis but also in the main-

tenance of hypertension in the early phases.

also a decrease of fibrinogen.

4. Industrial out-patient clinics. In the initial stages of hypertension, emphasis is placed by the Russian clinicians on alterations in the mode of life and adjustment in occupational activities as the most important therapeutic factors. This is a logical corollary of the generally accepted thesis that neuropsychiatric disturbances play a major role in the genesis and the development of hypertensive disease. The family environment is beyond the physician's immediate and effective control. Consequently, the technic of industrial out-patient clinics and "preventoria" has been utilized as means for creating living conditions which would reduce, temporarily, the stresses of life. The Russian terminology is to provide conditions "affecting favorably the patient's nervous system."

These "clinics" include overnight sanatoria to which the workers report at the end of the day's work. It is recommended that hypertensive individuals get good rest and plenty of sleep at night (eight to nine hours), avoid heavy physical work, assembly work carried out at great speeds, as well as work associated with severe mental strain and great responsibility. Attention is being paid, at least in theory, to the organization of occupational work of the hypertensive patient. Brief interruptions of the work routine, in the form of rest pauses, are introduced for therapeutic reasons. The physician may recommend a change of shift from

night to day and the elimination of overtime. Day preventoria ("prophylactoria") enable the patient to take from one to two hours of rest away from work during the day. In the combined day-night preventoria the workers receive medical care, drug treatment and meals (with reduced fat, salt and water intake). The period of treatment varies from one to three months. The results are encouraging. For instance, Beliaeva and Bitkova ²²¹ reported good results (subjective improvement and drop of blood pressure) in 47 out of 60 hypertensive workers treated in daytime prophylactoria, in 132 out of 168 patients treated in night prophylactoria, and in 92 out of 100 treated in the combined day-night type. The successfully treated patients were in the first and second stages, and the refractory cases in the second and third stages of hypertension.

Experience with the therapy provided in the framework of industrial outpatient clinics was described in greater detail by Beliaeva.²²² At the outset, blood pressure measurements were made in two factories. The total number of subjects was not indicated, but 341 individuals, mostly skilled workers, were identified as having definite hypertension, and there were 268 borderline cases (hyperreactors, persons with symptoms of hypertension but with blood pressure close to the upper limit of the norm); 43% of the hypertensives were below 40 years of age. The majority of the hypertensive patients (74%) were in the early phase of the disease, 18% in the "stable" phase, and 8% in the "sclerotic" phase (according to Miasnikov's system of classification). Both groups were followed systematically, with examinations scheduled at intervals of from one to two months.

In taking down of the case histories, special attention was paid to the influence of occupational factors on the course of the disease. Attitudes toward work and complaints about specific aspects of work (monotony, speed of the operations, demands for constant attention, noise) were registered. This information was to serve as an aid in achieving a better adaptation of the workers to occupational work.

Detailed recommendations were made to patients regarding proper rest and diet, participation in light sports (depending upon the development of the disease), and use of alcohol. Smoking was strictly prohibited. Individuals with more advanced hypertension were given medical treatment or sent to preventoria, Houses of Rest and sanatoria.

The number of individuals who coöperated satisfactorily with the industrial clinic appears to be small (90, i.e., about 26%). However, it should be noted that these individuals were followed up for from three to four years. Table 4 presents the results obtained in this group of "coöperators" and in 100 "non-coöperators." The initial number of individuals at different stages of hypertension was similar. The author concludes that this type of treatment, focused principally on altering the patient's mode of life and including occupation readjustment, is effective, especially in patients in the initial stages of hypertension. It is also considered to be of value as a preventive measure. No data on the latter point were offered.

It should be noted that the return of the blood pressure to "normal," or the disappearance of subjective symptoms under this system of treatment, does not mean that full health has been restored. Unfavorable alterations in the mode of life are likely to elicit again both objective signs and subjective symptoms of hypertension.

TABLE 4

Changes in Blood Pressure and Subjective Symptoms Among 90 "Coöperators" (C) and 100 "Noncoöperators" (NC) Over a Period of Three to Four Years.

(All values are given in percentages (Beliaeva, 228 tables 1 and 2))

Changes in Blood Pressure

Stages of Diseases	Nur	nber		ease to	Some I	Decrease	No Change		Inci	ease
Diseases	C	NC	С	NC	С	NC	С	NC	С	NC
IA IB	12	8	8	3	_	_	5	4		1
	37	44	17	5		-	19	34	- 1	5
IIA	37	30	2	-	8	1	24	26	2	3
IIB	13	14			1		12	12		2
IIIA	1	3		-	-	- 1	1	2	_	1
IIIB	-	1	-		-	-	-	-	-	1
Total	100%	100%	27	8	9	1	61	78	3	13

Subjective Symptoms

Stage of Disease	Impro	vement	No C	hange	Deterioration	
	С	NC	С	NC	С	NC
IA	7	2	5	5		1
IB	20	6	16	33	1	5
IIA	17	2	19	25	1	3
IIB	3	_	10	14		-
IIIA	or the same of the	-	1	2	-	1
IIIB	-	-	_	-	-	1
Total	47	10	51	79	2	11

5. Local blocking. A transient ligature of the nerve-vascular bundle around the temporal artery, avoiding complete arterial occlusion, improved cerebral symptoms in the majority of 166 hypertensive patients.²²⁸ The subjective improvement in the first month after the ligature was rated excellent in 38, and as good to fair in 102; only 26 patients did not respond. In 44 patients reëxamined two years later the results were still excellent in 10 and good in 27; in only seven patients was a beneficial effect absent. In a follow-up study, Zhirmunskaya and Sherman 224 noted some parallelism between electroencephalographic changes and clinical improvement. The skin pain threshold decreased in 28 out of 63 patients. Acoustic threshold and the amplitude of pulsation in the volume plethysmogram of arms or legs decreased in the majority of patients, and hypertensive headaches disappeared. However, there was no correlation between clinical improvement and the changes of blood pressure. The procedure is suggested mainly for hypertensive patients with pronounced headaches, and appears to rest mainly on empiric grounds. A simpler treatment, proposed by Sitalev, 225 is Novocain injection in several zones of the scalp; the results were encouraging.

Novocain injection around the carotid sinus produced an immediate fall of blood pressure in the initial stage of hypertension. In a comparison of various locations for the Novocain block,²²⁷ the paranephric location was found to be most effective. While this treatment may produce in some patients a pronounced

fall of blood pressure for a short period, chronic results (observation for from

six to 13 months) were disappointing.

The largest series (142 patients) with paravertebral Novocain block was reported by Davidov.²²⁸ The results were, in general, favorable in essential but not in nephrogenic hypertension. The author recommends the procedure because of its simplicity, lack of side-effects, and relative good prospects of success.

It may be pointed out that paravertebral alcohol injections had been used by Levy and Moore ²²⁹ for relief of cardiac pain in 1931, but at present this type of treatment seems to be used in the U.S.S.R. more frequently than elsewhere.

6. Oxygen therapy. Following Kedrov's suggestion (see Section V), Liberman ²⁸⁰ used oxygen therapy in patients with essential hypertension and cerebral symptoms (headaches, vertigo, noise sensation, etc.), after confirming and enlarging Kedrov's animal experiments. In anesthetized cats, hypoxia increased arterial blood pressure and, to a much greater extent, intracranial pressure and pulsations (up to 13 times the initial amplitude), whereas breathing a 70% oxygen mixture had the opposite effect. The patients stayed from one to one and one-half hours in a chamber with 50 to 65% oxygen every day for a period of two weeks.

The immediate effect of the first treatment was a relief of headaches in the majority of 100 patients which lasted several hours. The reaction of the blood pressure was not uniform. The effects after two weeks of treatment were excellent. In 88 out of 91 patients in the first and second stages of hypertension, the headaches were considerably relieved or disappeared completely. In no case was there any deterioration. Five out of eight patients in the third stage reported an improvement. The reaction of the blood pressure was not uniform (decreased in 36, increased in 12, unchanged in 52). No data were available about the duration of the improvement.

VIII. EPILOGUE

A review limited to investigations carried out within any one country cannot be fully satisfactory, since integration of information derived from all sources is needed to arrive at a balanced picture of the contemporary status of research in a particular segment of science. The justification for this review lies mainly in the barrier of language, physical inaccessibility of the widely scattered materials, and fundamental differences in emphasis and in conceptual frame of reference. Unquestionably, in the U.S.S.R. the scientists are paying more attention to the problem of vasomotor control by the central nervous system than are their Western colleagues, who concentrate more on the hemodynamic, electrophysiologic and biochemical factors.

Actually, the Russian work on essential hypertension may serve as a show-case exhibit of the need for the integration of scientific information on a world-wide basis. In an excellent article, "A Guide to the Theory of Arterial Hypertension," which appeared just at the completion of the present review, Page, McCubbin and Corcoran 281 discussed critically the potential role of disturbance of the carotid sinus reflexes and the neurogenic (sympathetic) vasoconstriction, together with other mechanisms involved in essential hypertension. However, no reference was made to the potential role of the central nervous system, particularly the cerebral cortex. In contrast, according to the Russian concept,

disturbance in the central nervous system is the primary factor in the patho-

genesis of essential hypertension.

Russian biomedical research lacks statistical sophistication, and, in clinical work, rigorous use of controls is usually missing. This is particularly unfortunate in the appraisal of various therapeutic regimens used for the treatment of hypertension, in which the subjective symptoms form an important part of the clinical status of the patient and are susceptible to improvement based on the power of suggestion. The temporary effects of procedures that may be labeled as "medicinal psychotherapy" are well known, and include the reduction of blood pressure resulting from the administration of pharmacologically inactive "medicines," such as the ingestion of water flavored with fruit juices, and of other forms of placeboes.

Nevertheless, the experimental documentation in the Russian technical literature of the importance of the central nervous system is impressive, and should have due impact on the theory of pathogenesis of essential hypertension.

This does not mean that the Russian concept should be accepted in toto. Experimental production of prolonged arterial hypertension by disturbance of cerebral cortical functions has been clearly demonstrated; however, it is not certain whether this applies to a minority or to a majority of hypertensive patients. While the Russian authors have clearly shown early changes in C.N.S. functions in patients with essential hypertension, further research is needed to elucidate whether this is primary or secondary development. Yet the reëxamination and recognition of the role of the C.N.S. in essential hypertension appear to be of theoretic as well as of clinical and possibly of diagnostic importance. The concepts and methods used in Russia on so large a scale should also be given consideration, to a greater extent than up to now, in the experimental work carried on outside the U.S.S.R. Should the present review be useful in this regard, we would feel adequately rewarded for a substantial amount of essentially "extracurricular" labor.

There are some signs and signals of change in the emphasis in the Western cardiologic literature, though they are as yet limited in scope. Specifically, in a recent editorial, while decrying as too facile the imputing of a "psychogenic" origin to the common cardiovascular diseases, Bach 282 stresses the role of the central nervous system as an important link in the chain of events resulting in cardiovascular disturbances. It appears appropriate to close this review by a citation (ibid., p. 326) of his statement calling for full recognition and adequate support of the efforts of cardiovascular and neurologic investigators alike in developing and sustaining a fruitful interest in the resolution of the problem of the vasomotor control by the central nervous system.

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CASE REPORTS

DERMATOMYOSITIS WITH PULMONARY LESIONS*

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Dermatomyositis is an inflammatory and degenerative disease of skin, muscle and, occasionally, other organs. The symptoms are characterized by weakness and tenderness of the affected parts, fever, cutaneous eruptions, edema, dysphagia and progressive wasting. Dermatomyositis is included among the "collagen" diseases, and it is often difficult to distinguish this condition from scleroderma and systemic lupus erythematosus. However, in contrast to the relatively frequent occurrence of pulmonary lesions in the other collagen diseases, the lungs have rarely been found to be involved in dermatomyositis as part of the basic disease. It is the presence of this feature which prompts the following case report. Noteworthy, too, in the present instance is the fact that, to our knowledge, this is the first reported case of dermatomyositis in which the nature of the pulmonary lesions was suspected during life, ascertained by lung biopsy and confirmed at autopsy.

CASE REPORT

A 62 year old white man developed numbness, redness and swelling of both hands in August, 1955. A month later he noted progressive weakness and anorexia, resulting in a 15-pound weight loss. In November, 1955, he began to note increasing shortness of breath, cough and expectoration of yellowish sputum which was occasionally blood-streaked. Shortly thereafter he had an acute seizure of chest pain, chills and fever. In spite of the administration of penicillin and tetracycline the symptoms increased and he was admitted to a hospital.

Of interest in the past history is the fact that at the age of nine years the patient had a protracted illness with joint pains, at which time, he recalled, his feet were swollen. Two years prior to the present illness he had a period of a "pins-and-needles" sensation in the fingers, and the hands were swollen and felt numb. In 1952 he had an attack of precordial distress, but no organic disease was found. He had been employed as a polisher and buffer of stainless steel. Information was obtained later to the effect that his children and grandchildren had various allergic conditions, including asthma, hay fever, penicillin sensitivity, infantile eczema and dermatographia.

On admission to the hospital the patient was acutely ill and cyanotic. Blood pressure was 120/80 mm. of Hg; temperature, 102° F.; pulse rate, 116 per minute. An eruption was noted over the face. There was subjective numbness of the right thumb, index and middle fingers, but no neurologic deficit. The lungs were clear to percussion, but on auscultation fine râles and rhonchi were heard throughout both lungs. The remainder of the physical examination revealed no abnormalities. Chest

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x-rays showed abnormalities which were interpreted as diffuse fibrosis, emphysema and bronchiectasis, with superimposed patchy pneumonic consolidation involving the base of the right upper lobe and the apical segment of the right lower lobe. Laboratory examinations showed 4,350,000 red blood cells, 7,800 white blood cells, and a normal differential; erythrocyte sedimentation rate, 86 mm. (Westergren). Urinalysis, fasting blood sugar, serology and cold agglutinins were negative. Total protein,

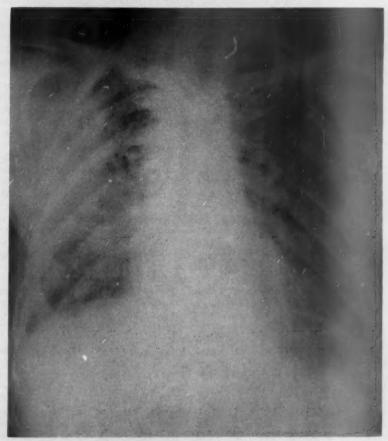


Fig. 1. December 19, 1955. Chest x-ray shows linear and patchy infiltration in both lungs and conglomerate infiltrations in right lung.

7.2 gm.; A/G ratio, 2.6/4.6. Smears, cultures and guinea pig inoculation of sputum and gastric contents failed to reveal acid-fast bacilli. Purified protein derivative (PPD) skin tests were negative in both strengths. The condition was ascribed to a viral pneumonia (figure 1).

The patient became afebrile on bed-rest alone, although the condition in the lungs showed only slight improvement. Four days after admission to the hospital he developed a generalized pruritus, with progressive scaling of the skin of the face,

abdomen and extremities. Three weeks after admission, his temperature rose to 104° F. He developed marked weakness, and the desquamation of the skin became more intense. He was treated with 1.2 million units of penicillin for two days, without effect. The temperature reached 105° F.; pulse rate, 104; respiration, 30 per minute. The patient was extremely weak, dyspneic and in a shocklike state; the

face was swollen, showing a bluish purple hue.

Because of his grave condition, the patient was given hydrocortisone intravenously, and this was followed by a drop in temperature within a few hours. The following day he was placed on oral cortisone, 100 mg. daily, continuous oxygen and intravenous feedings. On this regimen the temperature vacillated, gradually leveling off to a normal range during the following 12 days. In addition to cortisone, the patient also received isoniazid, streptomycin and Ilotycin. Thirty days after admission, and nine days after the acute episode, it was noted that the patient had an extensive exfoliative dermatitis, most severe over the shoulders, scapulae and hips, and an erythema multiforme bullosum-like eruption in the mouth. His general condition improved slowly, and cortisone was discontinued after 40 days. During this period, and in subsequent weeks, the patient noted difficulty in chewing and swallowing, also hoarseness, weakness of the extremities, and stiffness of the hands. He was discharged three and a half months after admission with a diagnosis of bilateral pulmonary infiltrations of undetermined etiology and hypersensitivity to penicillin.

The patient noted increasing dyspnea and weakness of all extremities associated with numbness of the fingers. The weakness became so severe that he could not lift his arms above his head, and had to grasp a cup with both hands to keep it steady. He could walk only with the aid of a cane. He had moderate cough and expectoration. On July 17, 1956, he consulted one of the writers (E. H. R.). At this time he showed marked muscle wasting, weakness and a generalized erythematous, dry, scaly rash over the body. A systolic murmur was heard at the mitral area. Blood pressure was 170/70 mm. of Hg. Fine râles were heard throughout both lungs, most marked at the bases. The extremities felt cold but were not swollen. The liver and spleen were not felt. The erythrocyte sedimentation rate was markedly accelerated. Other features of the physical and laboratory findings will be detailed shortly. The chest x-ray revealed diffuse, linear, interstitial striations throughout both lungs (figure 2). It was suspected that the pulmonary lesions were part of a generalized basic disturbance, probably dermatomyositis. The patient was admitted to the Montefiore Hospital on August 2, 1956.

Physical examination revealed a chronically ill-looking man in no acute distress. The face was taut, expressionless and covered by an erythematous, dry, scaly eruption (figure 3). Over the back, shoulders, buttocks and thighs there were symmetric, well demarcated, circular, scaly, erythematous, shiny, atrophic and depigmented areas. The trachea was deviated to the right. The neck veins were flat, and there was no thyroid enlargement. Indirect laryngoscopy showed no vocal cord paralysis. The chest showed slight increase in the posteroanterior diameter, with intercostal retraction on deep inspiration. The percussion note was hyperresonant. Fine râtes were present in both lungs which did not clear on cough; there was also an occasional inspiratory wheeze. The heart revealed no abnormalities. Blood pressure was 110/70 mm. of Hg. Abdominal examination was negative. The extremities revealed pallor of digits from proximal interphalangeal joints distally. There was a chronic paronychia of the right third finger. Bilateral encysted hydroceles and

moderate prostatic enlargement were also found.

Neuromuscular examination showed (1) wasting of the temporal and masseter muscles without overt weakness; weakness of all cervical muscles; other cranial muscles, normal; (2) marked wasting of muscles at the shoulder girdles and glutei, disproportionately so for the general wasting present; (3) marked weakness at the

shoulder girdles, slightly less so in the arms, and marked weakness of the pelvic girdle musculature, with good strength of quadriceps and all muscles distal thereto; (4) flexion contractures of shoulders and elbows, and (5) deep tendon reflexes intact and no pathologic reflexes.

Chest x-ray examination revealed diffuse, interstitial striations and nodulations throughout both lung fields, especially in the right; prominent hilar markings, and accentuation of the horizontal fissure. Gastrointestinal x-ray examination revealed

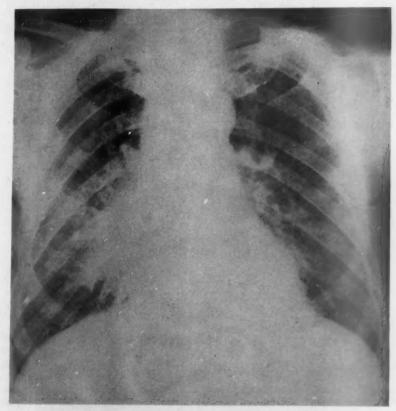


Fig. 2. July 17, 1956. Chest x-ray shows diffuse linear infiltrations permeating both lungs. (Later chest x-rays showed increase infiltrations, also cardiac enlargement.)

a hiatal hernia of the sliding type with some narrowing at the junction of the esophagus and hernia. These findings were considered to be consistent with those of a peptic esophagitis, shortening of the esophagus and associated hiatal hernia. The condition was also considered to be in keeping with a collagen disease. Fairchild camera views of the swallowing act revealed delay in propulsion of the bolus, retention and poor admixture of the barium, increased mucus content and some apparent churning effect. These observations, although nonspecific, were consistent with those found in dermatomyositis. Barium enema, gall-bladder series and intra-

venous pyelogram failed to reveal evidence of disease. There was no evidence of subcutaneous calcifications in the soft tissues.

Laboratory examinations included hematocrit, 38.5%; white blood cells, 6,600, with a differential count of polymorphonuclear cells, 58%; stab forms, 2%; lymphocytes, 34%; monocytes, 2%; eosinophils, 2%. The platelets were adequate in number. Erythrocyte sedimentation rate (Westergren) was 105 mm. The specific gravity of the urine was 1.010, with a trace of albumin; the sediment showed many red blood cells. Urea clearance was 56 c.c. per minute (73%); phenolsulfonphthalein, 61% excretion in one hour. The blood chemical constituents (urea nitrogen, fasting

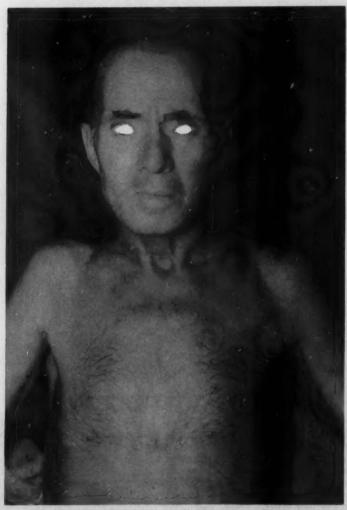


Fig. 3. Face and chest: taut expression, pigmentation of skin, atrophy of shoulder muscles. (The upper back showed areas of depigmentation.)

glucose, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus and alkaline phosphatase) were all within normal limits. Total protein, 9.0 gm.; A/G ratio, 2.9/6.1; repeated, 9.2 gm. and 2.3/6.9. Electrophoretic pattern revealed marked increase in gamma globulin. Transaminase, 75 units. Uric acid, 6.9; bromsulfalein, 3% retention in 45 minutes. Serum aldolase, normal. Serologic test for syphilis, negative. L.E. preparations were negative on three occasions. Old tuberculin (O.T.) skin test negative, 1/100,000 through 1/100. Stool guaiac test, negative. Sputum, negative for acid-fast bacilli. Twenty-four hour urine creatine, 0.460 gm.; creatinine, 0.584 gm. Tensilon* test, negative. Radioiodine uptake (RAI), 27% (euthyroid). Pulmonary function tests revealed a vital capacity of 2,400 c.c.; maximal breathing capacity, 81 L. per minute. There was no evidence of alveolar capillary block. The electrocardiogram showed RSR with occasional premature beats of the ventricle. A Kveim test for sarcoidosis was negative.

A lung biopsy revealed the pleural surface to be somewhat thickened and fibrotic. There were scattered foci throughout the pulmonary parenchyma, in which there was thickening of the alveolar septa by increased amounts of fibrous connective tissue. There was also a focal increase in the perivascular and peribronchial connective tissue and mononuclear cell infiltration (figure 4). Cultures of lung tissue for acid-fast bacilli and fungi were negative. A lymph node biopsy

revealed fibrous replacement of the architecture of the gland.

Biopsy of skin and muscle from the right pectoral region, obtained at the time of the lung biopsy, revealed an inflammatory infiltrate within the interstitial connective tissues of the muscle surrounding both the arterioles and the venules. This infiltrate consisted mainly of mononuclear cells which appeared to infiltrate the vascular wall of the involved structures, but did not appear to involve the muscle fibers directly, which were intact, with maintained striations and nuclei. There was a moderate increase in the collagenous connective tissue of the skin. The small vessels of the dermis had a surrounding inflammatory infiltration consisting of plasma and mononuclear cells similar to those seen in the muscle. A second biopsy of the right deltoid area revealed preservation of the normal structure of the muscle fiber bundles, with no appreciable degree of degeneration or atrophy. However, the sarcolemmal nuclei were quite prominent throughout, with a mild degree of myositis consisting of focal infiltration of the muscle and interstitial tissue with mononuclear cells. These inflammatory cells were also seen in the perivascular connective tissue.

The patient was placed on Meticorten, 10 mg. daily. Three days later he noted less stiffness and weakness in the shoulders, hands and legs. The Meticorten was continued, with considerable subjective but little objective improvement. A mild degree of euphoria developed. The patient was discharged on October 8, 1956, and thereafter was examined periodically by both writers. In February, 1957, there was a recurrence of weakness, loss of weight, and inability to carry on, and the patient was rehospitalized on March 11, 1957. The physical and laboratory findings showed no significant changes from those noted previously. He was treated with Terramycin and Meticorten, with some subjective improvement. On April 12, 1957, he underwent several dental extractions. Two days later he complained of pain at the extraction sites. A week later the temperature rose to 103° F., and the physical examination now revealed an increase in coarse râles in both lungs. In spite of vigorous antibiotic treatment, the patient went downhill and died on April 24, 1957.

The autopsy, performed by Dr. Alvin Lebendiger, revealed the following: Each pleural cavity contained about 100 c.c. of clear serous fluid. The thyroid was unremarkable and weighed 30 gm. The right lung weighed 1,125 gm. and the left lung, 1,025 gm. Both organs exhibited a very firm consistency, and on cut section revealed widespread pulmonary fibrosis and emphysema. The emphysematous com-

^{*} Hoffman-La Roche, Inc., a brand of edrophonium chloride.

ponent was most marked in the lower lobes, where the parenchyma showed a diffuse, spongy appearance. The process seemed to be most severe in the left lung. Histologically, there was evident destruction of the pulmonary architecture due to a marked increase in the amount of interstitial fibrous tissue, with obliteration of alveolar septa

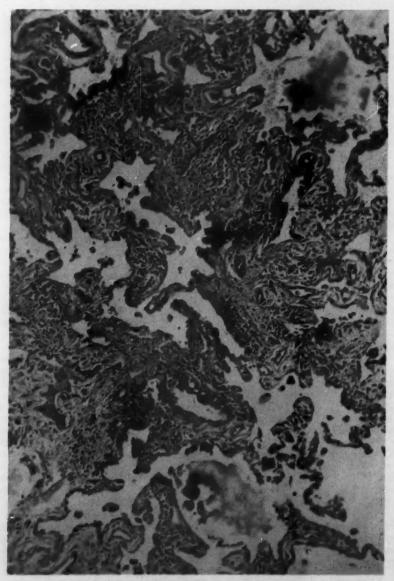


Fig. 4. Lung (biopsy): thickened alveolar septa, diffuse interstitial fibrosis, focal exudates of mononuclear cells (×150).

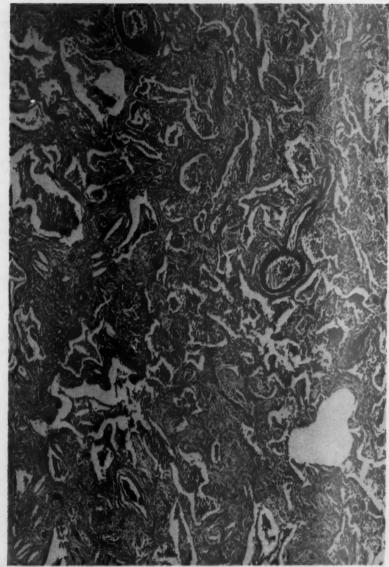


Fig. 5. Lung (autopsy): diffuse interstitial fibrosis with active production of fibrous tissue, plugs of tissue filling some of remaining alveoli; widespread epithelial proliferation; bronchiolectasis and emphysema (×80).

and alveoli. The interstitial fibrous tissue had a cellular appearance and seemed in a state of active production. Some persisting alveolar spaces were filled with either a fibrinous exudate or plugs of a cellular fibrous tissue of the type seen in organizing pneumonia. Numerous bronchioles were ectatic, and areas of well de-

veloped emphysema of persisting alveolar spaces were seen. The small arteries exhibited a hyperplastic sclerosis of the walls, with edema apparent as a separation of the layers of fibrous and smooth muscle tissue. Occasional arteries also showed an exudate of mononuclear cells within their walls, without fibrinoid necrosis (figure 5).



Fig. 6. Muscle (autopsy): atrophy, fragmentation and loss of striation of muscle fibers; mononuclear cell infiltration (×200).

The heart weighed 425 gm. There was no excessive pericardial fluid and no evidence of pericarditis. The increase in weight of the heart was due to a well developed cor pulmonale with hypertrophy and dilatation of the right ventricle. The pulmonary conus measured 12.5 cm. in circumference (normal maximum, 8 cm.). The coronary arteries exhibited no significant degree of arteriosclerosis. Although the myocardium appeared unremarkable grossly, there was microscopic evidence of widespread interstitial fibrosis of a type not necessarily secondary to vascular disease. However, the additional microscopic finding of a hyperplastic sclerosis of the small myocardial arteries raised the question as to whether the interstitial fibrosis was the result of vascular disease of the small arteries or of an antecedent myocarditis.

The liver weighed 1,700 gm. and was unremarkable. The spleen weighed 300 gm. and was grossly congested. The pancreas was unremarkable grossly and microscopically. The entire gastrointestinal tract was unremarkable grossly. Microscopic examination of the esophagus revealed a replacement of a good portion of the muscularis by dense scar tissue. There was no appreciable increase in the amount of fibrous tissue within the submucosa. The right adrenal gland weighed 7 gm., and the left, 6 gm. Except for some thickening of the periadrenal small arteries and lipid depletion, these glands were unremarkable. The kidneys weighed 200 gm. each and were unremarkable.

Section of skeletal muscle revealed a focal prominent exudate of mononuclear cells including histiocytes, lymphocytes and plasma cells in the interstices. Occasionally these exudates were perivascular in location. Within these areas of inflammatory reaction there were focal atrophy, fragmentation and loss of striation of muscle fibers. There was some degree of atrophy, manifested by an increase in the number of muscle nuclei and by a thinning of the muscle fibers (figure 6).

The skin of the forehead and cheeks revealed grossly a mottled reddish appearance. Elsewhere the skin appeared thinned and covered by a fine scale. No other lesions were evident at autopsy grossly. Histologically the picture was one of atrophic scarring of the dermis with loss of dermal appendages. The epidermis was also atrophic with a loss of rete pegs.

The anatomic diagnosis was dermatomyositis with involvement of skin, muscle, heart and esophagus; interstitial myocardial fibrosis; diffuse organizing interstitial pneumonitis, bilateral; pulmonary arteritis; bronchiectasis and emphysema; cor pulmonale.

Discussion

There is little doubt that the patient presented findings in keeping with dermatomyositis. One was dealing with a bilateral, symmetric, nonsuppurative polymyositis associated with dermatitis, Raynaud's phenomenon, progressive muscular atrophy and weakness.^{1, 2} Noteworthy was the occurrence of pruritus and progressive scaling of the skin following penicillin administration. The possible role of allergy in initiating or causing a systemic disturbance of the type reported has been mentioned with reference to other collagen diseases, including dermatomyositis.^{5, 4} The laboratory findings revealed an increased excretion of creatine in the urine and a greatly lowered creatinine coefficient, as well as elevated transaminase and uric acid, indicative of muscle destruction.^{5, 6} There was elevation of the serum globulin and of erythrocyte sedimentation velocity. The histopathologic changes in the skin and muscle, including the fragmentation and loss of striation of muscle fibers, the mononuclear cell infiltration and the increase of interstitial connective tissue, although not specific for dermatomyositis, are in keeping with a collagen disease.^{7, 8}

The roentgen examination revealed interference in the swallowing mechanism.

with retention of the barium at the esophagogastric junction. When the patient was re-admitted seven months later the esophageal distention was even more prominent. At autopsy the esophagus revealed replacement of a portion of the muscularis by scar tissue. The chest x-rays in the initial stages of the disease showed bilateral patchy infiltrations with conglomerate areas in the right midlung region. Later the infiltrations became more diffuse, stringy and interstitial, similar to the lesions seen in the other collagen diseases, notably scleroderma, systemic lupus erythematosus, polyarteritis, rheumatoid disease, 9-12 and in occasional instances of the Hamman-Rich syndrome. 18 The lung biopsy and subsequent findings at autopsy showed thickening of alveolar septa and increase in perivascular and peribronchial connective tissue, and diffuse bronchiolectasis and emphysematous honeycombing, a picture obtained in the chronic stages of several collagen diseases affecting the lungs.14, 18 Noteworthy also was the presence of a hyperplastic sclerosis of small arteries without fibrinoid necrosis. The temporary symptomatic improvement following administration of steroids has been observed in other members of the collagen group of diseases, including dermatomyositis. 15, 16

In the literature on dermatomyositis there is frequent reference to the fact that, as a result of muscular impairment of mastication, swallowing and esophageal reflux, as well as diaphragmatic involvement, aspiration pneumonia occurs. Rarely do descriptions of the roentgen findings mention diffuse miliary or nodular infiltrations which might conceivably reflect the presence in the lungs of a systemic disease. 17, 18 In a discussion of the pulmonary lesions in dermatomyositis, 19 one of the writers mentioned the fact that a careful search of the literature did not reveal any reported instances of dermatomyositis with pulmonary lesions as part of the basic disturbance. It was suspected, however, that with increasing use of chest x-rays and greater awareness of the systemic nature of the collagen diseases, instances of dermatomyositis with pulmonary lesions would be found.

The suspicion expressed was shortly confirmed by a case of dermatomyositis with pulmonary lesions published by Mills and Mathews.²⁰ A 52 year old woman presented signs and symptoms in keeping with dermatomyositis, although the usual features of the disease were not marked. The chest x-rays showed widespread interstitial infiltrations within the parenchyma of the right lung and, to a lesser extent, of the left lower lobe. At autopsy the lung tissue was found to be markedly altered, showing quite extensive patchy collapse, interstitial or interalveolar fibrosis, and a mild interalveolar and interstitial chronic inflammatory cell infiltration. There were dilated bronchioles in the collapsed and fibrotic area, the bronchial epithelium being extensively degenerated and some of the expanded lung tissue showing congestion and edema. The present case is the second one to be reported in which the pulmonary signs and symptoms were the presenting features and constituted an important part of the patient's disease.

SUMMARY

The case is reported of a 62 year old white man who showed characteristic symptoms, physical signs and laboratory findings of dermatomyositis. The course of the disease at the onset was featured by an atypical pneumonia. In time, the lungs revealed diffuse interstitial fibrosing lesions, bronchiolectasis

and emphysema. Skin, muscle and lung biopsies showed changes in keeping with a systemic disturbance of the nature of dermatomyositis. The postmortem examination showed dermatomyositis with involvement of skin, muscle, heart and esophagus; diffuse organizing interstitial pneumonitis; pulmonary arteritis, bronchiectasis and emphysema; interstitial myocardial fibrosis, and cor pulmonale.

ACKNOWLEDGMENT

We wish to thank Dr. Robert G. Bloch and Dr. Harry M. Zimmerman for their cooperation in making the clinical and pathologic material available. We are indebted to Dr. Alfred J. Bernstein, of the Bronx Hospital, New York City, for the use of figure 1.

SUMMARIO IN INTERLINGUA

Le discussiones de dermatomyositis in le litteratura contine frequente referentias al facto que pneumonia per aspiration occurre in casos de ille condition, resultante de dysfunction muscular del mastication e del inglutition e etiam de affectiones diaphragmatic. Del altere latere, il es rar que descriptiones del morbo mentiona diffuse infiltrationes miliari o nodular in le pulmones como parte del pathologia systemic. Es reportate un caso de dermatomyositis con lesiones pulmonar in que istos esseva suspicite de constituer un parte del disturbation fundamental. Le diagnose esseva confirmate per biopsia pulmonar e plus tarde per constatationes necrootic.

Un homine de racia blanc de 62 annos de etate deveniva malade in augusto 1955 con insensibilitate, rubescentia, e inflation de ambe manos. Un mense plus tarde ille notava grados progressive de debilitate, anorexia, e perdita de peso. Ille experientiava dyspnea, tusse, e expectoration, e brevemente postea ille suffreva un accesso acute de dolores thoracic, algor, e febre. Le constatationes physic e roentgenographic esseva ascribite a un pneumonia virusal. Subsequentemente le patiente disveloppava crescente grados de debilitate muscular, insensibilitate digital, febre de basse grado, prurito generalisate, progressive squamiformation erythematose in le pelle facial e abdominal con desquamation, e un eruption in le bucca que resimilava erythema multiforme bullose. Le examine neuromuscular revelava marcate grados de atrophia muscular in le cinctura scapular, debilitate, e un certe grado de contractura flexional in le scapulas e cubitos. Examines laboratorial monstrava un augmentate excretion de creatina in le urina, un grandemente reducite coefficiente de creatinina, elevate nivellos de transaminase e de acido uric, e augmentate valores pro globulina seral e pro le sedimentation erythrocytic. Biopsias de pelle e de musculo revelava fragmentation e perdita de striation in le fibras muscular. Un biopsia pulmonar monstrava spissification de septos alveolar, augmentos del histos conjunctive perivascular e peribronchial, e diffuse bronchiolectasis. Le examine post morte confirmava le diagnose de dermatomyositis con affection de pelle, musculo, corde, e esophago; diffuse pneumonitis interstitial organisante, arteritis pulmonar, bronchiectasis, e emphysema; fibrosis myocardial interstitial e corde pulmonal.

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THE SYNDROME OF EXOPHTHALMOS, HYPERTROPHIC OSTEOARTHROPATHY AND LOCALIZED MYXEDEMA: A REVIEW OF THE LITERATURE AND REPORT OF A CASE *

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Although hypertrophic osteoarthropathy has been noted in association with a wide variety of primary disorders, its occurrence with diseases of the thyroid has been little mentioned in the literature. In 1919 Ebstein briefly reported a case of clubbing of the fingers developing in a 24 year old male following thyroidectomy for exophthalmic goiter. Thomas in 1933 described in detail a patient who, eight months after having had a subtotal thyroidectomy for exophthalmic goiter, developed progressive hypertrophic osteoarthropathy and

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a concurrent brawny and pigmented edema of the legs consistent with myxedema. Thomas felt that the rapid change in thyroid function following surgery resulted in changes in peripheral blood flow which initiated the process of hypertrophic osteoarthropathy. Cushing in 1937 briefly reported a case of typical Graves' disease who developed hypertrophic osteoarthropathy seven years after thyroidectomy. This patient also had swelling of the legs. Four years later Rynearson and Sacasa 5 described another similar case. This was a patient who was subjected to thyroidectomy for exophthalmic goiter and developed clubbing six weeks later associated with a brawny, irregular nonpitting edema of the legs. In 1942 Mendlewitz 1 mentioned having seen a patient with congestive heart failure due to Graves' disease who subsequently developed clubbing. Greene 6 in 1951 reported a case of exophthalmos, enlarged thyroid and clubbing. This patient later developed pretibial myxedema and marked progression of his exophthalmos and hypertrophic osteoarthropathy. Greene also mentioned another patient he had seen who had severe exophthalmos and clubbing, but x-rays did not show periosteal new bone formation. He pointed out that all the cases occurred in males and were associated with severe exophthalmos and with hypothyroidism. Most recently Levitt,7 in his book on the thyroid, mentions a patient with severe malignant exophthalmos, hypertrophic osteoarthropathy and localized edema of the legs. He felt that the pituitary gland was the etiologic factor. The following case report is one of hypertrophic osteoarthropathy with an accompanying localized myxedema following thyroidectomy for Graves' disease.

CASE REPORT

A 24 year old white male was first seen with the chief complaint of yellowness of the skin and eyes of one week's duration. He stated that he had been well until four years before, when he noted the onset of weakness, nervousness, increase in bowel movements to three to four times a day, and weight loss despite a tremendous appetite. At this time he also noted increasing thickness of his neck and protuberance of his eyes. All of these symptoms progressed, and three years before he was seen he was told he had an overactive thyroid, and allegedly was given two courses of radioactive iodine. However, because he did not improve he went elsewhere six months before being seen. At that time he was hospitalized, put on iodine and antithyroid medication, and after two months underwent a subtotal thyroidectomy. He was given several blood transfusions and did very well, gaining weight and feeling fine. Two weeks before being seen (four months post-transfusions) he developed nausea, vomiting and anorexia, and one week later noted the onset of jaundice, light stools, dark urine, pruritus and loss of desire to smoke.

His family history was significant in that his mother had had a thyroidectomy for a toxic nodular goiter two years previously, and had also had a cholecystectomy for cholecystitis. His father was alive and had chronic pulmonary insufficiency with bronchitis and emphysema. He had two brothers and one sister, all alive and well.

His past history revealed that he had had rheumatic fever as a child, a tonsillectomy, and an appendectomy for acute appendicitis. He smoked one pack of cigarettes daily and drank no alcohol.

On physical examination his temperature was 99.6° F.; pulse, 72; respirations, 18; blood pressure, 130/80 mm. of Hg. His skin and sclerae were moderately icteric. The palms were moist and cool. His eyes showed marked exophthalmos. The pupils were negative. Extraocular movements and funduscopic examinations

were normal. There was a healed red scar at the base of the neck. A few small, discrete axillary, inguinal and epitrochlear nodes were palpable. The lungs were clear to auscultation, and the heart was unremarkable. The liver extended two fingerbreadths below the right costal margin and had a sharp, smooth, tender edge. The spleen tip was felt below the left costal margin. There was a well healed scar in the right lower quadrant of the abdomen. Examination of the rectum and extremities was entirely normal. The neurologic examination was negative. The urinalysis revealed a specific gravity of 1.022, pH 6.0, no albumin and no sugar.



Fig. 1. Right hand.

It was positive for bilirubin. The hemoglobin was 14.5 gm.; red blood count, 4,610,000/cu. mm., white blood count, 9,300/cu. mm., with 58% mature polys, 3% bands, 38% lymphocytes and 1% eosinophils.

A diagnosis of homologous serum hepatitis was made and the patient was hospitalized. In the hospital further laboratory data revealed a bilirubin of 12.16 mg.%, with direct reacting, 2.71 mg.%, and indirect reacting, 9.45 mg.%. The total protein in the blood was 6.75 gm.%, with an albumin of 3.65 gm.% and a globulin of 3.10 gm.%. The thymol turbidity was 3.50 Maclagan units; cephalin flocculation, 3 plus at 24 hours and 4 plus at 48 hours. The alkaline phosphatase was 9.0 King-Armstrong units. The patient remained in the hospital for six weeks and did very well, the jaundice gradually receding. His urine became negative for bilirubin. The serum bilirubin went down gradually until on discharge it was 0.6 mg.% total. The thymol turbidity dropped to 2.14 units; total protein, 6.6 gm.%, with an albumin-

globulin ratio of 4.1/2.5 gm.%; alkaline phosphatase, 3.9 units; cephalin flocculation, negative. The cholesterol was 130 mg.%, with esters 108 mg.%; creatinine, 1.1 mg.%; sedimentation rate, 4 mm. per hour; heterophil agglutination, negative; basal metabolic rate, minus 4; serologic test for syphilis, negative. Urine culture was negative. X-rays of the chest, skull, lumbosacral spine and retrograde pyelograms were all normal. An electrocardiogram was normal. An electrocardiogram was negative. Radioactive isotope studies revealed an uptake of 59% and a clearance of 45 ml. per minute, representing a high normal. The patient was discharged asymptomatic.



Fig. 2. Left hand. Fusiform soft tissue swellings and periosteal proliferation.

He got along well for the next two months but then, following an unhappy love affair, became extremely depressed and attempted suicide. He was hospitalized at a psychiatric institution, where a diagnosis of psychoneurosis with reactive depression was made. He apparently did well with psychotherapy and remained there for four months. It was during his last month at the psychiatric institution (one year post-thyroidectomy) that he first noted the onset of swelling of his fingers and the pretibial areas of his legs. There was no pain, but his fingers became stiff. This became progressively worse, and he was seen shortly after discharge.

On physical examination his blood pressure was 108/68 mm. of Hg; pulse, 80. He was well developed and nourished. The skin was cool and dry. His head was unremarkable. There was a moderate exophthalmos with lid lag present. The ears, nose and throat were negative. There was a well healed thyroidectomy scar at the base of the neck. No lymphadenopathy was felt. His lungs were clear to percussion

and auscultation. His heart was not enlarged, there was normal sinus rhythm, and no murmurs were heard. The abdomen revealed a well healed appendectomy scar. On examination of the extremities fusiform swellings were noted between the proximal and distal interphalangeal joints, and between the proximal interphalangeal and metacarpophalangeal joints. The joints themselves were not involved in the swelling giving them a dimpled appearance. The swelling was firm, deep, hard, nonpitting, not movable and nontender. No clubbing was noted. No skin changes were present. Swellings were present over the middle third of the tibial bones of the lower extremities. The skin in these areas seemed red and thickened, with prominent pores, giving a pigskin appearance. There were discrete, salmon-colored papules about ¼ cm. in diameter involving the areas of swelling and extending laterally as well. These papules were firm, elastic, nontender, and movable with the skin, and were compatible with localized myxedema. Rectal and neurologic examinations were unremarkable.

The hemoglobin was 13.5 gm.; red blood count, 4,9000,000/cu. mm.; white blood count, 8,000/cu. mm., with a normal differential. Urinalysis was unremarkable. The blood calcium was 10 mg.%; phosphorus 2.9 mg.%; alkaline phosphatase, 1.7 Bodansky units; total serum protein, 6.9 gm.%; prothrombin concentration, 100%. Basal metabolic rate was plus 7. Radiographic examination of both hands (figures 1 and 2) revealed fusiform soft tissue swellings surrounding the phalanges of the fingers and particularly involving the proximal phalanx of the left index finger, but not surrounding the interphalangeal joints. Periosteal proliferation and calcification were seen involving the shafts of many of the bones. The most pronounced changes were in the first and fifth metacarpals bilaterally, in the proximal phalanges of both thumbs. and in the proximal phalanx of the left fourth finger. The bony architecture was otherwise normal in appearance, with normal trabecular markings. There was no apparent abnormal tufting of the distal phalanges. The impression was chronic proliferative periostitis (chronic hypertrophic osteoarthropathy). X-rays of the chest were unremarkable. X-rays of the dorsolumbar spine, pelvis, other long bones and skull were negative. Thirteen months after the onset of his hypertrophic osteoarthropathy and localized myxedema, the patient was hospitalized again because of an increase in symptoms of nervousness and irritability. Physical examination revealed a blood pressure of 136/60 mm. of Hg; pulse, 96; temperature, 99.6° F. He was hyperkinetic, his skin was warm but dry and exophthalmos and a lid lag were obvious. His lungs were clear, the heart and abdomen were unremarkable, and there was no change in the findings of his extremities save for a fine tremor of the outstretched hands. The white blood count was 9,680/cu. mm.; hemoglobin, 18 gm.; red blood count, 5,320,000/cu. mm. An erythrocyte sedimentation rate was 7 mm./ hour; urinalysis, negative; stool, guaiac, 1 plus. Mazzini's test was negative; blood calcium, 11.2 mg.%; phosphorus, 3 mg.%; alkaline phosphatase, 4.3 Bodanski units; uric acid, 5.5 mg.%. A serum protein electrophoresis revealed a normal pattern. The basal metabolic rate was plus 9% and plus 14%, but the protein-bound iodine was 9.4 mg.% and the I181 uptake was 61%. X-rays showed no further changes in the periosteal bone formation, and a chest plate was negative. A biopsy of the skin over the tibia revealed that the dermal layer appeared to be widened, and between bundles of collagen there was a granular eosinophilic precipitate. This precipitate was mucicarminophilic, and the lesion was consistent with the diagnosis of localized myxedema. Pulmonary function studies showed a normal vital capacity, with no evidence of air trapping. The maximal breathing capacity was reduced slightly to 90% of the predicted value and showed no evidence of bronchial obstruction. The arterial blood was unsaturated to 93% at rest, but on exercise rose to 97%. The pCO2 was normal. The patient was given 2.44 mc. of I181, followed in 48 hours by the institution of thyroid, 0.15 gm., and propylthiouracil, 0.01 gm. three times a

day. However, he stopped this medication of his own accord after three weeks. He was followed monthly over the next five months, and gave the impression of still being slightly toxic. A basal metabolic rate was plus 11%, but an I¹⁸¹ uptake was

54%, and he was given an additional 2.5 mc. of radioactive iodine.

There had been no change in the soft tissue swellings over the areas of hypertrophic osteoarthropathy in the hands or over the areas of pretibial myxedema. Elastic bandages were applied tightly to the soft tissue swellings of a finger and leg. This had no noticeable effect. Then 150 turbidity-reducing units of hyaluronidase were injected into the area of pretibial swelling and an elastic bandage was applied. There was complete disappearance of the swelling by the next day. Similarly, 50 turbidity-reducing units of hyaluronidase were injected into the area of swelling of a finger and an elastic bandage was applied. No change occurred in the lesion. Following this, 150 µg of 1-triiodothyronine were crushed and mixed in 15 gm. of U. S. P. hydrophilic unguentine base. This ointment was applied to the pretibial area, which had returned to its original soft tissue swelling, and also to the soft tissue swelling of the finger. Elastic bandages were then applied. By the next day there was a marked decrease in the swelling over the pretibial area, but no change in the area over the finger. This was repeated later, using only the hydrophilic base, and no changes occurred. The patient is now doing well two months after his last dose of I131, with no change in the hypertrophic osteoarthropathy; the pretibial myxedema is kept down by local applications of 1-triiodothyronine and elastic bandages.

DISCUSSION

The etiology of hypertrophic osteoarthropathy is unknown. It has been seen in association with a wide variety of primary diseases, but only rarely with diseases of the thyroid. It was noteworthy in this case to see it develop after thyroidectomy for Graves' disease, and to find in the literature a few other cases of similar coincidence. Of further interest is the establishment of the presence of an accompanying localized myxedema. The gross appearance of the skin changes and of the soft tissue swelling in the pretibial areas of this patient is quite consistent with pretibial myxedema. The microscopic sections showing mucinous infiltration, although admittedly nonspecific, are further evidence that the lesion is compatible with this diagnosis. Finally, the response of the pretibial swellings to the local injection of hyaluronidase, as shown by Bloom et al., simultaneously by Grais, and later verified by Rosman, in contrast to the lack of response to similar injections into the soft tissue swellings associated with the hypertrophic osteoarthropathy, makes it quite apparent that localized myxedema as well as hypertrophic osteoarthropathy is present. When the literature on the previous cases is reviewed, it is seen that all of them mentioned a brawny, irregular edema of the legs compatible with localized myxedema.

It is probably fair to assume that this syndrome of exophthalmos, hypertrophic osteoarthropathy and localized myxedema is more common than the literature attests to. In a review of 34 cases of hypertrophic osteoarthropathy seen at the hospital, 11 one case was found associated with a burned-out goiter with exophthalmos. Since radiologically demonstrable periosteal proliferation of the long bones may be asymptomatic, 12, 13 and since pretibial plaques may be missed if not looked for, careful search for this syndrome might give a more

nearly exact estimate of its incidence.

Hyaluronidase injected locally is the only effective means known of decreas-

ing the swelling associated with localized myxedema. Its disadvantage is the necessity of frequent local injections, which are often painful. L-triiodothyronine was applied locally in the form of an ointment because of its effect at a cellular level. It was effective in this case, and is certainly worthy of further trial.

SUMMARY

1. A case is reported of a syndrome characterized by exophthalmos, hypertrophic osteoarthropathy and localized myxedema.

2. It is suggested that careful search in cases of exophthalmos, including radiologic survey of the bones, might well show that this syndrome is not so rare as is indicated by the literature.

3. The use of 1-triiodothyronine locally was an effective means in this case of reducing the swelling of pretibial myxedema, and deserves further trial.

ACKNOWLEDGMENT

I wish to thank Dr. Sidney Werner for obtaining radioactive iodine studies, pulmonary function studies and biopsy of the pretibial lesion. I am also grateful to Dr. David P. Barr for his criticisms

SUMMARIO IN INTERLINGUA

Ben que osteoarthropathia hypertrophic ha essite notate in association con un extense varietate de disordines primari, su occurrentia con morbos del thyroide es mentionate infrequentemente. In un revista del litteratura mundial, io ha succedite a discoperir solmente octo casos de iste association. Ha essite signalate previemente que omne iste casos es definitemente etiam casos de ophthalmia. Tamen, le presentia de un myxedema localisate como parte de iste syndrome clinic ha remanite relativemente ignorate. In tres del octo casos trovate in le litteratura, le description non esseva sufficientemente detaliate pro determinar si o non myxedema localisate esseva presente in illos. Tamen, in le altere cinque, le descriptiones publicate rendeva apparente que un edema del gambas—non molle, non retenente depressiones digital—esseva presente, in compatibilitate con le diagnose de myxedema localisate.

Es describite in detalio le caso de un masculo de 24 annos de etate, qui disveloppava osteoarthropathia hypertrophic e myxedema pretibial septe menses post thyroidectomia pro morbo de Graves. Roentgenogrammas del mano revelava chronic periostitis proliferative del metacarpales e phalanges, con tumescentia molle del histos, in compatibilitate con le diagnose de osteoarthropathia hypertrophic. genogrammas del areas pretibial esseva negative, a parte le presentia del tumefaction de histos molle. Biopsia del area pretibial revelava un lesion compatibile con le diagnose de myxedema localisate. Injectiones local de hyaluronidase in le areas pretibial causava un disparition rapide del tumefaction. Per contrasto con illo, nulle simile responsa sequeva le injectiones local de hyaluronidase in le tumefacite histos molle del manos. Esseva concludite que myxedema localisate e etiam osteoarthropathia hypertrophic esseva presente. Es opinate que iste syndrome de exophthalmia, osteoarthropathia hypertrophic, e myxedema localisate es minus rar que su representation in le litteratura. Viste que le radiologicamente demonstrabile proliferation periosteal del ossos longe pote esser asymptomatic e viste que le placas pretibial escappa facilemente al observation, il es probabile que un cerca meticulose pro iste syndrome resultarea in un plus exacte estimation de su incidentia.

Le application local de I-triiodothyronina (in le forma de un unguento) al myxedema pretibial succedeva in iste caso in reducer le tumefaction.

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SARCOIDOSIS WITH VERTEBRAL INVOLVEMENT *

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The protean manifestations of sarcoidosis are well known. Involvement of practically every organ and system of the body, including the bones, has been well documented. Vertebral sarcoidosis, however, appears to be surprisingly rare. Biopsy of vertebral bone marrow at autopsy has been reported in several cases as showing the typical noncaseating granulomatous lesions. 1, 2, 3 These reports, however, have had no correlation with antemortem symptomatology or roentgenographic examinations. Because autopsy data in sarcoidosis come from an extremely small group of patients and because microscopic examination of vertebral bone marrow is not a routine procedure in most autopsies, any conclusions drawn from an analysis of postmortem data concerning the incidence of vertebral involvement might be misleading.

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Forrestier and Robert a reported a single case in which the diagnosis of sarcoidosis was confirmed by mediastinal lymph node biopsy, with the subsequent appearance of decalcification of the thoracic and lumbar vertebrae and definite deformities of the second and third lumbar vertebrae. This case eventually required fusion of the lumbar spine, but biopsy was not taken, so that the diagnosis of sarcoidosis of the vertebral column was made by inference.

To our knowledge, the following case is the first in which a definite antemortem diagnosis of vertebral sarcoidosis has been made.



Fig. 1. Preoperative laminagram of eleventh and twelfth thoracic vertebrae, showing extensive lytic lesion.

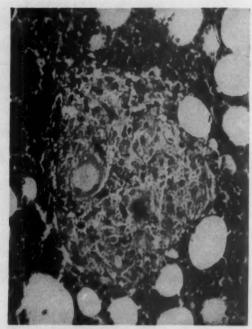


Fig. 2. The lytic lesion of the eleventh thoracic vertebra obtained by biopsy, revealing the noncaseating granuloma.

CASE REPORT

A 33 year old Negro was admitted to the Medical Service of the Veterans Administration Hospital on July 20, 1955. In 1952 an abnormality had been detected during a routine roentgenologic examination of the chest. He was hospitalized at another institution, at which time a diagnosis of sarcoidosis was made on the basis of a biopsy of a cervical lymph node. He remained asymptomatic until two months prior to admission to this hospital, at which time he developed chronic low back pain which did not respond to therapy with cortisone.

On admission to the hospital the patient was an acutely ill young male. His temperature was 102° F.; blood pressure, 100/64 mm. of Hg. The liver was just palpable at the right costal margin. Numerous small cervical, axillary and inguinal lymph nodes were palpable.

Laboratory studies were within normal limits with the exception of the serum proteins, which showed total protein of 7.9 gm. per 100 ml., with 2.9 gm. albumin and 5.0 gm. globulin. Roentgenogram of the chest disclosed bilateral hilar adenopathy. There was a diffuse reticular pattern involving both lung fields, thought to be consistent with the diagnosis of sarcoidosis. Tuberculin and fungus skin tests were negative. Lateral planigrams of the vertebral column revealed a lytic lesion of the eleventh and twelfth thoracic vertebrae (figure 1). This was then thought to be most likely tuberculous. Roentgenograms of the hands and feet were within normal limits, and aspiration of the sternal bone marrow revealed only evidence of increased erythroid activity.

The patient's course in the hospital was marked by recurrent febrile episodes

associated with bouts of paralytic ileus. On August 24, 1955, a retroperitoneal exploration was performed, with no abnormal findings. Biopsy of a lymph node at that time revealed nonspecific reticular hyperplasia.

Serial planigrams of the thoracic vertebral lesion revealed rapid progression of the lytic process, and on March 27, 1956, biopsy of the eleventh thoracic vertebra and fusion of the thoracolumbar spine was carried out. The biopsy revealed noncaseating granulomata consistent with sarcoidosis (figure 2). Special stains for acid-fast bacilli were negative. Cultures for tubercle bacilli, fungi and pyogenic organisms revealed no growth. Review of the lymph node from the biopsy performed in 1952 confirmed the diagnosis of sarcoidosis (figure 3).

On several occasions during the patient's hospitalization his fever responded dramatically to cortisone therapy, but prolonged steroid treatment was felt inadvisable.

Following spinal fusion, the patient did well and was discharged with a back brace. He returned to the hospital in February, 1957, at which time follow-up planigrams of the involved vertebrae revealed marked healing (figure 4). At this time the patient was asymptomatic and on no specific therapy.

DISCUSSION

The diagnosis of sarcoidosis can rarely be made with certainty by the clinician, radiologist or pathologist alone. Multiple infectious or mineral agents can mimic both the roentgenographic and the microscopic findings. It is felt, however, that in the case presented the diagnosis of sarcoidosis with destructive vertebral involvement has been definitely established.



Fig. 3. Photomicrograph of the cervical lymph node from biopsy performed in 1952.



Fig. 4. Postoperative laminagram of eleventh and twelfth thoracic vertebrae, showing marked healing of lytic process.

It is recommended that more extensive bone surveys by roentgenogram be performed in patients with this disease. In addition, in the differential diagnosis of a destructive vertebral lesion sarcoidosis should be considered. Appropriate microscopic and bacteriologic studies of specimens obtained by needle biopsy or operation should be employed in these cases to avoid the erroneous diagnosis of Pott's disease.

SUMMARY

We have presented what we believe to be the first case of a definite antemortem diagnosis of sarcoidosis with vertebral involvement. The addition of sarcoidosis to those diseases considered in the differential diagnosis of destructive vertebral lesions and more extensive roentgenographic bone surveys in sarcoidosis are suggested.

SUMMARIO IN INTERLINGUA

Ben que sarcoidosis es un morbo characterisate per su capacitate de afficer multe differente systemas, incluse le skeleto, lesiones vertebral es mentionate in solmente rar casos in le litteratura.

Le patiente del presente reporto pare esser le prime in qui le diagnose histologic de sarcoidosis vertebral esseva facite ante morte. A parte le affection de nodos lymphatic e del pulmones, lesiones de character lytic esseva notate roentgenographicamente in le dece-prime e le dece-secunde vertebra thoracic. Biopsia de nodos lymphatic revelava alterationes compatibile con le diagnose de sarcoidosis. Le patiente haveva un invertite proportion de albumina a globulina, e tests cutanee a tuberculina e fungo esseva negative.

A causa del evidentia roentgenographic de un extension del lesiones vertebral, un fusion del columna thoracolumbar esseva effectuate. Biopsia revelava granuloma non-caseante. Tincturationes special pro bacillos acido-resistente e culturas pro bacillos de tuberculose, pro fungos, e pro organismos pyogene esseva negative.

Es suggerite que sarcoidosis deberea esser prendite in consideration in le diagnose defferential de destructive lesiones vertebral e que iste typo de affection deberea esser investigate in patientes qui suffre cognoscitemente de sarcoidosis.

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SEVERE INFECTIOUS MONONUCLEOSIS TREATED WITH PREDNISOLONE *

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INFECTIOUS mononucleosis is a disease of undetermined etiology which generally pursues a benign course. Consideration of specific therapy is rarely required. However, fatalities due to infectious mononucleosis have been reported. Fatal cases include those with complications such as Guillain-Barré

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syndrome, diffuse neurologic involvement, respiratory obstruction, splenic rupture and generalized "toxemia." s

Treatment of infectious mononucleosis is symptomatic. However, reports of cortisone- and corticotropin-treated mononucleosis can be found in the literature. In many, treatment was started because of serious complications in which death seemed imminent; these included neurologic involvement,⁶ respiratory obstruction ⁷ and generalized "toxemia." ⁸ In each situation a prompt and dramatic response to hormone therapy occurred.

This report concerns a severe case of anginose infectious mononucleosis successfully treated with prednisolone.

CASE REPORT

The patient was a 16 year old white girl first seen by us on September 14, 1956. Six days earlier she had noted the sudden onset of severe bilateral sore throat, without nasal symptoms but associated with malaise and fever. She was seen by her family physician, who started intramuscular penicillin, which she received for three days. The sore throat worsened, so that swallowing solids became impossible. Complete nasal obstruction occurred, causing mouth breathing which further increased the discomfort. Tetracycline, 250 mg. every six hours, was then started, without noticeable effect.

The patient was first seen at home. At that time she appeared acutely ill and was obviously dehydrated. Mouth breathing was apparent. Her temperature was 102.8° F.; pulse, 120; respirations, 28 and shallow. She had a pink, macular morbilliform rash on the upper thorax, neck and chin. The conjunctivae were injected. The fundi were normal. Each side of the nose was filled with thick, tenacious, non-purulent mucus which could not drain into the pharynx because the choanae were completely obstructed by greatly enlarged adenoids which bulged into each posterior naris.

The tongue was dry and furred. Both tonsils were greatly enlarged, and each was completely coated with a thick, matted gray exudate. There was no peritonsillar swelling at this time, and the uvula was not greatly swollen. The pharyngeal mucosa was injected but not edematous, and there was no question of an impaired airway. The neck was held extended and resisted flexion. The lymph nodes of the anterior and posterior cervical chains were 1 to 3 cm. in size, firm, movable and moderately tender. No other nodes were palpable. The lungs were clear. The heart was not enlarged to percussion. The rhythm was regular. No murmurs were heard. P_2 was louder than A_2 .

Examination of the abdomen failed to reveal hepatomegaly or splenomegaly, although there was moderate tenderness and resistance to palpation in both upper quadrants. The extremities were negative, as was neurologic examination, including Kernig's sign.

Laboratory examination at that time revealed 12,200 white blood cells with 55% lymphocytes, many abnormal, of the type characteristic of infectious mononucleosis. The heterophil antibody titer was positive at a dilution of 1:256.

The patient was admitted to Emergency Hospital that night. Supportive therapy including intravenous fluids was instituted. During the next 24 hours her condition deteriorated. Spiking temperature continued. Local discomfort increased. The patient, although never comatose, was obtunded and lethargic, and lay in a position of opisthotonos. The pharyngeal edema increased so that the tonsils almost met in the midline. The uvula was three or four times its normal size because of inflammatory edema, and the entire pharyngeal mucosa was so swollen that respiratory

Table 1

Laboratory Findings in a Severe Case of Infectious Mononucleosis

	9/14*	9/14	9/15	9/17	9/24
Hgb. (gm. %)	12.0	12.3	12.6	12.0	12.0
WBC	12,200	7,600	7,600	6,400	3,800
Lymph. %	55	15	17	13	40
Atypical lymph. %	Many	43	35	7	6
Mono. %	16	5	0	15	16
Eos. %	1	0	0 .	0	7
Baso. %	0	0	0	0	0
Poly. %	28	37	48	65	31
Heterophil	1:256	-	1:1,792	.:	1:896
Guinea pig absorption	1.200		1:448	100	1:224
Ox-blood hemolysin			1:256		
Bilirubin, 1 min. mg. %			0.3†		0.3
Bilirubin, total mg. %					0.9
Thymol turbid. (u.)			5.01		4
Ceph. floc.			1.3† 5 3+		
Urine bile		4+	37		2-

* Pre-admission.

† Result questionable. Patient was deeply jaundiced.

obstruction appeared to be imminent. The lingual tonsils were markedly enlarged. Stridor did not occur. In addition, the patient was obviously jaundiced, and bile appeared in the urine.

Laboratory findings are listed in table 1. Chest x-ray was negative.

The situation appeared desperate, and it was thought that the patient might die. It was therefore decided to institute steroid therapy. During the next 18 hour period, 50 mg. prednisolone in 2 L. of dextrose were infused intravenously.

The response was dramatic. Within 12 hours of institution of therapy the temperature fell to normal. The patient became alert and cheerful, and was able to accept oral food and fluid. Improvement in nasal obstruction was noted almost immediately. Pharyngeal edema was obviously reduced.

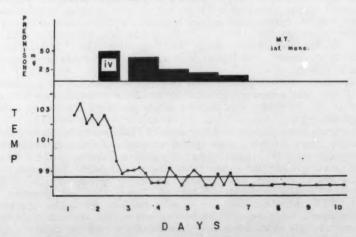


Fig. 1. Effect of steroid on temperature in severe infectious mononucleosis.

Oral prednisone was continued according to the dosage schedule recorded in figure 1. The patient received antibiotic "coverage" with tetracycline during the period of hormone administration. She remained essentially afebrile and asymptomatic. By the fourth day of treatment the tonsils appeared to be perfectly normal. The cervical adenopathy was diminished, although the posterior cervical nodes could be palpated until discharge. The remission was sustained after discontinuance of hormone therapy, and the patient was discharged after 10 days, completely asymptomatic, with very little if any residual malaise or asthenia.

DISCUSSION

A severe case of infectious mononucleosis has been presented. It was reasonable to believe that the patient might die. She was extremely toxic, and upper respiratory obstruction was progressing. Although lumbar puncture was not done, central nervous system involvement seemed likely. In fact, the findings here were very similar to those in the fatal case reported by Shinton and Hawkins.⁵

Rationale for institution of prednisolone resided in the known lympholytic action of adrenal steroids.

The response to therapy was dramatic, and comparable to that previously reported in the literature. It appears likely that the absence of severe asthenia, usually experienced during convalescence, might be related to the therapy.

SUMMARY

A case of severe anginose infectious mononucleosis is presented. Prognosis appeared to be poor. Treatment with prednisolone caused prompt, dramatic and sustained relief.

SUMMARIO IN INTERLINGUA

Es presentate un caso sever de anginose mononucleosis infectiose. Le patiente esseva un puera de 16 annos de etate. Su mononucleosis infectiose esseva inequivoc e confirmate per observationes hematologic e serologic. Illo causava un quasi complete obstruction nasal e pharyngee. In plus, le patiente monstrava signos de un affection hepatic e de toxemia generalisate, incluse manifestationes in le systema nervose central. Le prognose esseva apparentemente multo disfavorabile in despecto del uso de supportative mesuras therapeutic. Esseva administrate prednisona per via intravenose, con effectos dramatic jam manifeste intra 12 horas. Le temperatura descendeva a nivellos normal. Le condition mental del patiente se clarificava, e le obstruction supero-respiratori se meliorava. Le continuation del medication, nunc per via oral, resultava in le complete restablimento del patiente intra quatro dies. Le argumentation que justificava le uso de prednisona se basava super le cognoscite action lympholytic de steroides adrenal. Altere casos de mononucleosis infectiose, con simile mesuras e effectos therapeutic se trova jam reportate in le litteratura.

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VENTRICULAR TACHYCARDIA: A CASE REQUIRING MASSIVE AMOUNTS OF PROCAINE AMIDE (PRONESTYL) FOR REVERSION*

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THE following case is being reported because of the huge and unprecedented amount of medications required to control successfully a desperate cardiac complication, i.e., paroxysmal ventricular tachycardia. It was fairly clear from the experience during one of the episodes in this case that the tachycardia of itself might prove fatal. This permitted us—and encouraged us—to use the massive amounts of medication that proved to be necessary to control a subsequent attack.

CASE REPORT

This 46 year old married machinist was admitted to the Peter Bent Brigham Hospital for the second time on June 27, 1957. He had apparently been in good health until March 20, 1956, when he suffered a well documented myocardial infarction, for which he was hospitalized in Amsterdam, N. Y. His recovery was satisfactory. In May, 1956, shortly after his discharge from the hospital, he spontaneously developed his first episode of paroxysmal rapid heart action. The pulse at the time is reported to have been 180 per minute and regular. His daily Digoxin was increased and quinidine was added. This episode of rapid heart action lasted for approximately one week.

Though the patient did not return to work, he did fairly well during the following months except for occasional episodes of paroxysmal rapid heart action, which responded rapidly to increases in his quinidine dosage. These episodes were spontaneous in onset, short in duration and not associated with chest pain or symptoms of congestive heart failure.

On January 25, 1957, the patient developed an episode of rapid heart action which

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proved resistant to the usual increases in quinidine. He was hospitalized in his home town and Digoxin and quinidine were pushed to tolerance, but the rapid heart action persisted. For the first time symptoms of overt congestive heart failure made their

When the patient was first seen at the Peter Bent Brigham Hospital (February 19, 1957), his condition was desperate. His pulse was 180 and regular; the systolic blood pressure was 95, with the sounds barely audible for a few millimeters at this level. Electrocardiogram revealed a ventricular tachycardia (figure 1). Pronestyl was immediately started intravenously, and after a total of 300 mg., given over a fiveminute period, the tachycardia reverted to a normal rhythm of 67 (figure 2).

On this admission the patient's condition was critical. It was doubtful at first whether he would survive more than another day or two. He had a most amazing stare to his eyes without any real exophthalmos. It seemed that the lids were so retracted that nothing but white sclerae was visible. This all disappeared within 48 hours. The pulse had been barely perceptible. A right thoracentesis was performed the morning after admission with removal of 1,000 c.c. of clear fluid. The lactic dehydrogenase on February 21, 1957, was 2,840 units. On February 23, February 25, March 1 and March 6 the readings were 136, 128, 138 and 106 respectively. After the heart rhythm had returned to normal the patient gradually improved, so that on discharge on March 9, 1957, he felt well and had no cardiac symptoms. He was advised to take Pronestyl, 0.25 gm. three times a day, Digoxin, 0.25 mg. once daily, and Dicumarol, about 50 mg. a day.

The patient remained free of symptoms and had no coronary pain, congestive heart failure or paroxysmal rapid heart action until June 24, 1957, when he was startled by a small girl's throwing rocks at the window of his motor car while he was driving. The patient immediately noted palpitation, which gradually increased to a maximum over a period of less than five minutes. He consulted his local physician, who attempted to control the paroxysmal rapid heart action by increasing the dosage of Pronestyl. This failed to revert the arrhythmia, and the patient was referred to the Peter Bent Brigham Hospital for the second time, three days later, on June 27, 1957.

Physical Examination: The patient appeared apprehensive but in no acute distress. Blood pressure, right arm, 90/75 mm. of Hg; left arm, 94/80 mm. of Hg. Radial pulse was 60 and irregular. The neck veins were not distended, but occasional large jugular venous pulsations were noted. The lungs were clear. The heart was not enlarged to percussion. The apical rate was 180 and was not affected by carotid pressure. The first heart sound varied slightly in intensity in different cycles, and alteration in the length of the heart cycles was noted at times. There was some increased resistance below the right costal margin. The spleen was not palpated. There was no dependent pitting edema.

Laboratory Data: Blood Hinton test was negative. Urinalysis, white blood cell count, differential count and hematocrit were within normal limits. The erythrocyte sedimentation rate was 17 mm. Blood chemical studies were not remarkable. Lactic dehydrogenase was 100 units (mean, 60) on July 2, 1957. Cephalin flocculation was 2 plus on July 4, 1957. Blood levels of epinephrine and norepinephrine were zero gamma per liter (normal, 0 to 1.5), and 5.5 gamma per liter (normal, 1.0 to 5.5), respectively. An electrocardiogram on admission showed ventricular tachycardia, with a rate of 171 and pronounced RST segment depression characteristic of subendocardial ischemia. X-rays of the chest on June 27, 1957, revealed no significant change in heart size compared to a previous examination on March 5, 1957. The lungs were negative. Repeat x-ray of the chest after reversion of the arrhythmia showed no significant change in the heart or lungs. Circulatory dynamics on June 28, 1957, revealed a venous pressure of 225 mm. and a circulation time of 25 seconds

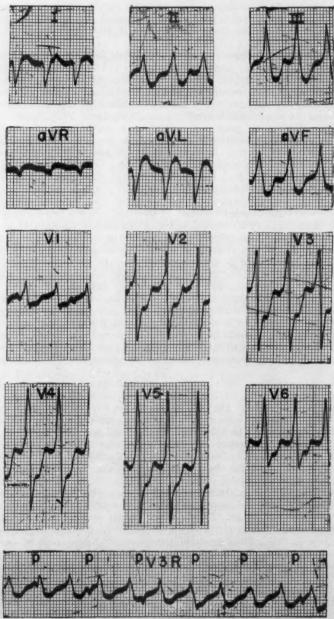


Fig. 1. Customary 12 leads as shown during the paroxysmal ventricular tachycardia (2/19/57, 2:00 p.m.). Lowest strip shows independent auricular rate of 100; ventricular rate is 160.

(arm-to-tongue). Vital capacity at this time was 2.4 L. Repeat studies on July 8, 1957, showed a venous pressure of 85 mm., a circulation time of 22 seconds, and vital capacity of 2.5 L. The patient's cardiac output was determined by Dr. Richard Gorlin and found to be 2.7 L. per minute on July 2, 1957, while in tachycardia, and 6.6 L. per minute on July 8, 1957, after reversion to normal sinus rhythm.

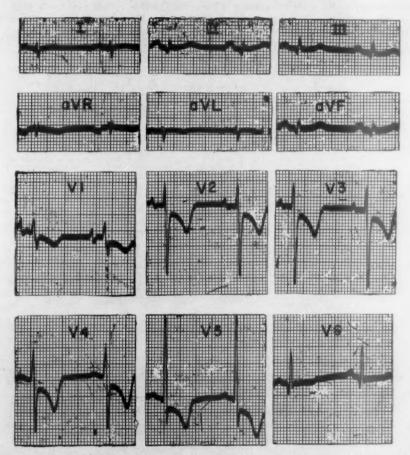


Fig. 2. Customary leads at 11:00 p.m., 2/19/57, show return of normal sinus rhythm with marked "post-tachycardia" anoxemic changes in the ventricular complex.

Hospital Course: This patient's clinical course centered around various measures employed in an attempt to revert the tachycardia to a normal sinus rhythm (table 1).

On June 28, 1957, he was given a 10 c.c. ampule of 1.0 gm. of procaine amide intravenously over a period of 20 minutes (50 mg. per minute). The ventricular rate fell from 180 to 140, but the ventricular tachycardia persisted. One and a half hours later the same dose was repeated in the same manner, without success. There were no subjective symptoms or change in blood pressure. After a slight temporary

slowing the original rate would return in about 20 minutes. Then he was put on

potassium chloride, 1.0 gm. four times daily by mouth.

On June 29, 1957, 2 gm. of procaine amide were given intravenously in 200 c.c. 5% dextrose in water (D/W) over a period of 20 minutes. The starting heart rate was 190 and the maximal slowing was to 140. One milligram of atropine was given intravenously at the point of maximal slowing but failed to reduce the rate further. The rate returned to 190 in approximately 15 minutes. There was no blood pressure change, but the patient experienced mild nausea and dryness of the mouth.

TABLE 1

Date	Type of Therapy	Effect on Ventricular Rate	Symptoms and Effect on Blood Pressure		
6/28/57 1 hr. later	Pronestyl, 1 gm. I.V. (50 mg./min.) Pronestyl, 1 gm. I.V. (50 mg./min.) Potassium chloride, 1 gm. p.o. q.i.d.	V. rate fell from 180 to 140, then returned to 180 each time in about 20 minutes	None		
6/29/57	Pronestyl, 2 gm. in 200 c.c. 5% D/W in 20 minutes I.V. (100 mg./min.) Atropine, 1 mg. I. V.	V. rate fell from 190 to 140. Atropine produced no change. Rate returned to 190 in about 15 minutes	Mild nausea and dryness of mouth.) No B. P. change		
6/30/57	Quinidine, 0.6 gm. in 200 c.c. 5% D/W in 35 minutes I.V. (17 mg./min.)	V. rate fell from 200 to 150, with alight increase in width of QRS. Rate returned to 200 in about 20 min.	None		
7/1/57	Potassium chloride, 60 mEq. (4.5 gm.) in 1,000 c.c. 5% D/W in 90 min. I.V. Pronestyl, 1 gm. I.V. (50 mg./min.) immediately after KCl	V. rate of 210 was unchanged during KCl infusion, fell to 170 with 760 mg. Pronestyl and no further change. Returned to rate of 210 in about 30 min.	None		
7/2/57	Pronestyl, 3 gm. in 300 c.c. 5% D/W in 30 min. I.V. (100 mg./min.) Neo-synephrine, 5 mg. in I.V. bottle Atropine, 0.5 mg. I.V. Neo-synephrine, 10 mg. I.M.	V. rate fell from 214 to 130, with marked widening of QRS com- plex after 2.0 gm. Pronestyl. Atropine produced no change	Nausea, skin clammy, B. P. fell from 90/80 to 70/50 but responded to Neo-synephrine		
7/3/57	Quinidine, 1.2 gm. in 250 c.c. 5% D/W in 60 min. I.V. (20 mg./min.) Atropise 1 mg. I.V. Neo-synephrine, 5 mg. I.V.	V. rate fell from 214 to 150. Atropine produced no change	Nausea and retching. B. P. fell from 90/80 to 70/? but responded to Neo-symphrine		
7/4/57	Magnesium sulfate, 4 gm. (8 c.c.) I.V. in 53 minutes	V. rate fell from 200 to 190	Sensation of warmth and flushing. No B. P. change or nausea		
7/5/57	Pronestyl, 4 gm. in 200 c.c. 5% D/W in 36 min. (111 mg./ min.) I.V. Neo-synephrine, 10 mg. I.V. Atropine, 1 mg. I.V.	V, rate fell from 200 to 140, with marked widening of QRS. Atropine given when V, rate was 140; 13 min. later (2 min. after Pronestyl infusion was completed) nodal rhythm with rate of 80 appeared	Fatigue, slight nausea. Sensa- tion of fullness in epigastrium and tingling over face. B. P. fell from 100/80 to 70/60 but responded to Neo-synephrine		

On June 30, 1957, quinidine, 0.6 gm., was given intravenously in 200 c.c. 5% D/W over a period of 35 minutes. The heart rate was initially 200, and the lowest rate achieved was 150, with a return to 200 in 20 minutes after the treatment. A slight increase in the width of the QRS was noted. There was no change in the blood pressure, and no nausea.

On July 1, 1957, potassium chloride, 60 mEq. (4.5 gm.) in 1,000 c.c. 5% D/W was given intravenously over a 90-minute period. This was followed immediately by 1 gm. of Pronestyl given intravenously over a period of 20 minutes. The initial heart rate was 210, and no change was observed during potassium chloride infusion.

After 700 mg. (14 minutes) of procaine amide the rate had fallen to 170 and no further reduction occurred. No blood pressure change or subjective complaint resulted.

On July 2, 1957, procaine amide, 3 gm., and 5 mg. Neo-synephrine were given intravenously in 300 c.c. 5% D/W over a period of 30 minutes. The starting heart rate was 214, and the slowest rate achieved was 130, after 2 gm. procaine amide.

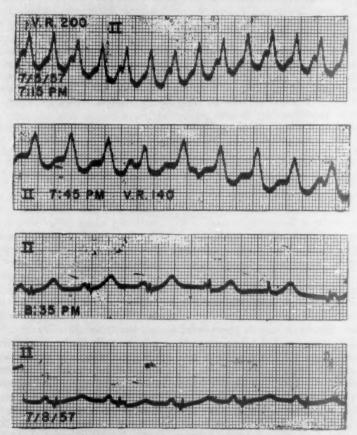


Fig. 3. Top tracing is typical of ventricular tachycardia. Second tracing shows slowing from Pronestyl (about 3 gm.). Third strip shows disappearance of ventricular tachycardia with inception of nodal rhythm. Lowest tracing shows normal sinus rhythm.

Atropine, 0.5 mg. intravenously, failed to produce further slowing. Marked widening of the QRS complex—from 0.11 or 0.12 sec. to 0.16 sec.—was noted. The blood pressure dropped from its initial 90/80 to 70/50 mm. of Hg, but responded to 10 mg. Neo-synephrine intramuscularly. The patient was noted to be sweating and pauseated

Neo-synephrine intramuscularly. The patient was noted to be sweating and nauseated. On July 3, 1957, quinidine, 1.2 gm., was given in 250 c.c. of 5% D/W over a period of 60 minutes. The starting heart rate was 214. One milligram atropine was given intravenously when maximal slowing had been achieved, but this failed

to reduce the rate below 150. The blood pressure fell from 90/80 to 70/? mm. of Hg, but responded to 5 mg. Neo-synephrine given intravenously. The patient experienced some nausea and retching.

On July 4, 1957, magnesium sulfate, 4 gm., was given intravenously over a 5½ minute period. This produced a transient change in heart rate, from 200 to 190, but did not affect the blood pressure. The patient experienced warmth and flushing but no nausea.

On July 5, 1957, procaine amide, 4 gm., was given intravenously in 200 c.c. 5% D/W over a period of 36 minutes. Gradual slowing of rate.—from 200 to 130—and marked widening of the QRS complex—from 0.11 or 0.12 sec. to 0.16 sec.—were noted. The blood pressure fell from 100/80 to 70/60 mm. of Hg, but responded to 10 mg. Neo-synephrine added to the intravenous solution. Atropine, 1 mg., was given intravenously when the rate had slowed to 140. The decrease in rate continued, and then a nodal rhythm of 82 was established 13 minutes after the atropine injection (figure 3). The patient experienced slight nausea, tingling around the mouth, fullness in the epigastrium and fatigue.

The following day an electrocardiogram revealed a normal sinus rhythm and signs of ischemia consistent with the "post-tachycardia syndrome." From then on the patient's progress was smooth and uneventful. He became ambulatory, had no symptoms, and was discharged on July 9, 1957, on quinidine, 0.3 gm. twice a day, Pronestyl, 0.25 gm. four times a day, a dose of Dicumarol sufficient to keep the prothrombin time around 20% of normal. He has been well as of December 1, 1958.

DISCUSSION

Paroxysmal ventricular tachycardia is generally a serious complication associated with grave forms of heart disease. Not infrequently it develops in the early days following the onset of acute myocardial infarction. It may also come in a transient form in patients who have long since recovered from acute coronary thrombosis. Very rarely it is found in otherwise healthy people having no evidence of organic heart disease or any other important disease. It occasionally is associated with valvular disease or other forms of organic heart disease. Finally, it may be precipitated by excessive administration of digitalis.

An extensive review of paroxysmal ventricular tachycardia has previously been published.1 The diagnosis of this condition is always important, and at times may be difficult. The following are the clinical features which characterize the condition. First, ventricular tachycardia is never altered or slowed by means employed to stimulate the vagus, i.e., carotid sinus or ocular pressure, or deep breaths, etc. Second, the rhythm, though often rapid and regular, may show slight irregularities in the length of the various cardiac cycles. Third, unlike classic paroxysmal auricular tachycardia, the heart sounds in different cycles may vary slightly in intensity. Fourth, on careful inspection occasional large jugular waves can be seen. These result when the auricles contract at the moment the ventricles are in systole. Accurate diagnosis eventually rests upon electrocardiographic interpretation. Even then at times it remains uncertain. It is difficult, if not impossible, to distinguish paroxysmal ventricular tachycardia from a condition in which the auricles are beating regularly and there is a paroxysmal A-V nodal tachycardia with temporary bundle branch block. Finding ventricular premature beats in electrocardiograms, when normal sinus rhythm is established, having the same general contour as the tracings

during the ventricular tachycardia, lends strong support to the diagnosis. There was very little doubt about the correctness of the diagnosis in this case.

The main lesson to be drawn from this experience is that heroic measures are at times necessary in therapy when the urgency of the situation permits them. This man, who had previously had an attack of coronary thrombosis, was desperately sick when first seen by us. He had developed paroxysmal ventricular tachycardia which persisted for 26 days. This is an unusually long duration for tachycardia of this type. He had already been given the oral medication customarily employed in this condition. He promptly reverted to a normal rhythm after a small dose of 0.3 gm. of Pronestyl intravenously. Certain features of this case remain unexplained. We have never seen such a peculiar and striking stare to a patient's eyes without exophthalmos. The extremely high level of lactic dehydrogenase, higher than anything previously obtained in our laboratory, remains puzzling. Finally, the ease with which we were able to control the arrhythmia when the patient was almost moribund stands in marked contrast to the extreme difficulty in regularizing the heart when he was in very good condition during a subsequent attack.

The second attack that we observed was directly precipitated by an emotional upset. When a youngster threw some stones at the window of his motor car palpitation promptly recurred, after he had felt well and been free from attacks for several months. The relation of emotion to paroxysmal ventricular tachycardia has been observed previously.2 When he was seen on this second occasion he really had no symptoms, looked quite well, and merely was aware of the rapid heart rate. The tachycardia had not lasted long enough to impair his health significantly. The previous spell had lasted almost four weeks and, because of the long duration and marked hypotension, a hydrothorax had developed. It became imperative to restore a normal rhythm as quickly as possible, since we knew that dire results could ensue if the tachycardia persisted long enough. One medication after another was tried in increasing amounts. Those that offered some prospect of slowing the tachycardia were potassium salts, magnesium sulfate, quinidine, and procaine amide (Pronestyl). They all have proved effective at one time or another in the past. Potassium chloride, 1 gm. four times daily orally, and even 4.5 gm. intravenously, proved unsuccessful. On another occasion 4 gm. of magnesium sulfate intravenously failed to restore the normal rhythm. Quinidine sulfate, 0.6 gm. intravenously on one day and 1.2 gm. intravenously on another day, also failed. Atropine sulfate was also given intravenously in combination with the other medications on the basis of a single experience that one of us had had many years ago. On that previous occasion giving 2 mg, atropine subcutaneously, at a time when the ventricular rate had been slowed by quinidine, promptly broke up the tachycardia of the ventricle.8 Similar doses of quinidine in that case had repeatedly failed when atropine had not been used.

Inasmuch as Pronestyl at present seems to be the most promising drug for this condition, and this patient was known to have responded once before to the intravenous dose of 300 mg., this medication was again tried. The standard intravenous doses customarily employed range from 200 to 500 mg. and occasionally as high as 1,000 mg.⁴ Pronestyl was therefore given in increasing doses of 1.0, 2.0 and 3.0 gm. intravenously on different days, but without success

(table 1). It was observed that the QRS complex had widened from 0.11 or 0.12 second to at least 0.16 second during the administration of 3.0 gm. Pronestyl. This increase of at least 33% in the duration of the ORS ordinarily would make one refrain from giving any more or any larger doses of the drug, but the clinical condition of the patient seemed to warrant pressing therapy further. Finally, in desperation, this patient was given 4 gm, of Propertyl in 200 c.c. of 5% D/W intravenously over a period of 36 minutes. During this infusion the blood pressure fell from 100/80 to 70/60 mm. of Hg. For this reason 10 mg, of Neo-synephrine were added to the infusion. Several minutes after this, and 25 minutes after the beginning of the therapy, 1 mg. atropine was also injected intravenously, at a time when the ventricular rate had dropped from 200 to 140. Several minutes later the ventricular tachycardia disappeared and a slow, peculiar nodal rhythm took its place. This later gave way to a slow, normal sinus rhythm. Thereafter everything progressed smoothly and the patient felt quite well. He was discharged on a program of quinidine, 0.3 gm. twice daily, Pronestyl, 0.25 gm. four times daily, and Dicumarol therapy.

The largest dose of Pronestyl previously reported, as far as we have been able to determine, is 3 gm. intravenously.⁵ This was unsuccessful in regularizing a case of auricular flutter. Whether the dose of 4 gm. given to the case reported here would have been successful without the additional use of atropine remains in doubt.

SUMMARY

A case of paroxysmal ventricular tachycardia is described in which one attack lasted 26 days but was readily controlled with a small intravenous dose (0.3 gm.) of procaine amide. The attack had produced extreme heart failure and marked hypotension, and almost proved fatal. With recovery the patient was quite well, but some months later another attack was precipitated by an emotional upset. This time, although his condition was still excellent, the tachycardia was refractory to all ordinary doses of medication employed. The heart was finally restored to a normal rhythm as a result of the unprecedented dose of 4 gm. of Pronestyl and 1 mg. of atropine given intravenously.

Although the huge doses of medication employed in this case cannot be recommended generally, and should be used with caution, there must be times, as illustrated by this experience, when they can be life-saving.

SUMMARIO IN INTERLINGUA

Tachycardia ventricular paroxysmal pote devenir un complication desperate de morbo cardiac. Ordinarimente illo pote esser dominate per medication de uso commun. Es presentate un caso in que iste arrhythmia non esseva alleviate mesmo per grande doses de procain-amido o quinidina. Reversion a un normal rhythmo sinusal esseva effectuate solmente post le injection intravenose de 4,0 g de procain-amido e 1,0 g de atropina. Le restablimento del patiente esseva excellente, e ille se ha mantenite in bon sanitate. Un revista del datos rende multo probabile que le tractamento usate salvava le vita del patiente. Il va sin dicer que le grande doses usate in le presente caso non pote esser recommendate generalmente e debe esser empleate cautissimente, sed il existe situationes—e le presente experientia offere un exemplo—in que tal doses preserva un vita que sin illos esserea perdite.

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EDITORIAL

UNILATERAL RENAL ISCHEMIA AS A CAUSE OF HYPERTENSION

THE relationship between renal ischemia and hypertension was first clearly demonstrated and brought to general notice by Goldblatt (1934). By applying a clamp to the renal artery so as partially to obstruct the circulation to the kidney, he was able to produce sustained hypertension in some dogs (and also monkeys) which had some clinical resemblance to essential hypertension in man. Release of the clamp or timely removal of the ischemic kidney usually resulted in prompt subsidence of the hypertension if the other kidney was normal. Something instrumental in increasing blood pressure is evidently elaborated or produced in increased quantity by the ischemic kidney.

As is now well known, such a pressor substance was isolated from both normal and ischemic renal tissue, a proteolytic ferment, renin, which acts on a globulin substrate in the plasma to produce a powerful pressor agent, termed angiotonin (Page), hypertensin (Braun-Menéndez) or, by mutual agreement, angiotensin.1 The structure of angiotensin has been determined and it has been synthesized.3

In spite of a very large amount of experimental work, the pathogenic significance of the renin-angiotensin system has not yet been established. It does appear to be operative in the acute stage of the hypertensive process that may follow unilateral renal injury, but as a rule virtually disappears after the chronic stage has been established. Assays of angiotensin have been made in human subjects, although the current methods are far too cumbersome for clinical use. For example, Skeggs et al. have reported a marked increase of angiotensin in human cases of malignant hypertension, but in benign essential hypertension the average quantities found were only slightly greater than normal and not convincingly significant. Braun-Menéndez 4 has announced that a new, much more sensitive method of assay has been devised and is being tested in his clinic, which should be of great value if it proves dependable. This work has not solved the problem of essential hypertension nor brought proof that it is renal in origin.

That unilateral renal disease in man can cause hypertension was first brought to general notice by Butler (1937), who reported that nephrectomy in a hypertensive subject with unilateral pyelonephritis was followed by

¹ Braun-Menéndez, E., and Page, I. H.: Suggested revision of nomenclature—angiotensin, Science 127: 242, 1958.

² Bumpus, F. M., Schwartz, H., and Page, I. H.: Synthesis and pharmacology of the octapeptid angiotonin, Science 125: 886, 1957.

³ Kahn, J. R., Skeggs, L. T., Shumway, N. P., and Wisenbaugh, P. E.: The assay of hypertensin from the arterial blood of normotensive and hypertensive human beings, J.

Exper. Med. 95: 523-529, 1952.

4 Braun-Menéndez, E.: The prohypertensive and antihypertensive actions of the kidney, Ann. Int. Med. 49: 717-731, 1958.

restoration of normal blood pressure. During the next several years many hypertensive patients with more or less clear cut unilateral renal injury were subjected to nephrectomy, often without much critical consideration as to their suitability. In a disappointingly large percentage of cases the hypertension was not influenced significantly, although in some cases a brilliant result was achieved. A large number of scattered reports was reviewed, perhaps a little too critically, by Smith in 1948 and again in 1956.5 Among 575 collected cases, a successful result was obtained in 26%, in the sense that the blood pressure remained below 140 mm. Hg systolic and 90 mm. diastolic for at least a year. If patients apparently cured but followed less than a year were included, the figure becomes 35%, but this is believed to be too high. A higher percentage of successful results should be obtained if better methods of selecting patients can be devised. Marked symptomatic improvement with substantial lowering of the blood pressure may be a highly satisfactory result clinically, even if the pressure does not fall to strictly normal figures.

In patients giving a favorable response, the fall in blood pressure may be almost immediate or more gradual over a few days, occasionally a few weeks. Instability of the pressure, rises in response to stress may be observed. Relapses may occur, usually within a few weeks or months, but

have been observed after more than a year.

Thompson and Smithwick ⁶ also stressed the infrequency of such cures. Among over 2600 hypertensive patients subjected to sympathectomy over a 14 year period, all thoroughly studied, only two cases of unilateral disease

were found who were cured at least one year after nephrectomy.

Of those patients who were relieved, a majority showed parenchymal lesions from chronic pyelonephritis; a minority, primary vascular lesions. The percentage of successful results among patients with vascular lesions, however, was much higher than that among those with pyelonephritis, a far commoner disease. The former included aneurysms and other congenital anomalies, pressure from tumors or fibrous bands on the pedicle, embolism of the renal artery or a large branch, but most often an atherosclerotic plaque involving either the aorta at the orifice of the renal artery or the latter vessel distal to the aorta. Thrombosis at such a point leading to infarction was a relatively frequent precursor of an acute attack of hypertension in this group.

The frequency of essential hypertension in the community is not precisely known. The frequency of unilateral renal disease among hypertensives is even less certain. Estimates have varied from 1 to 5%. If only a fourth to a third of these can anticipate a successful result from operation, the net reduction in the number of hypertensives in the community will be small.

⁵ Smith, H. W.: Unilateral nephrectomy in hypertensive disease, J. Urol. 76: 685-701, 1956.

⁶ Thompson, J. E., and Smithwick, R. H.: Human hypertension due to unilateral renal disease, with special reference to renal arterial lesions, Angiology 3: 493-505, 1952.

EDITORIAL

among the pyelonephritics.

Certain clinical features noted in many of the successful cases have been pointed out, especially by Perera and Haelig.7 The onset is often relatively abrupt in a subject with previously normal blood pressure, but occasionally in one with a previously benign essential hypertension. The disease tends to run a severe rapid course with high diastolic pressure like the accelerated or malignant phase of ordinary hypertension. The onset may be marked by headaches, progressing rapidly to outspoken manifestations of encephalopathy and retinopathy with visual disturbances and grave retinal arteriolar changes. Generalized renal involvement develops, with albuminuria and particularly, according to Deming,8 polyuria, polydipsia and impaired concentrating power, attributed to a lessened capacity of the tubules to reabsorb water, sodium and chloride. Others have been less impressed by these latter features. The disease may begin at any age, but an onset before 20 or after 50 is highly suggestive, since ordinary essential hypertension rarely begins at these ages. Such features are not diagnostic but may suffice to select subjects for more extensive special and burdensome investigations.

The disease may be precipitated by trauma to the renal region, accidental or surgical. In case of embolism or thrombosis of the renal artery there is often an acute attack of pain in the flank or lower abdomen which may simulate renal colic or be mistaken for appendicitis and lead to unnecessary operation. Such a history is very important, as is also a known source of emboli. In certain subjects known to have a normal blood pressure at the time of such an attack, hypertension has developed within a few days 9 or even a few hours after trauma.10, 11 Severe hypertension with encephalopathy and retinopathy can develop within three weeks,12 often within six weeks to three months.13 In others, however, a much longer interval may

be observed.

Tests of total renal function are of no help except to detect severe bilateral disease which would preclude nephrectomy and usually contraindicate further elaborate procedures. Moderate impairment would not necessarily

⁷ Perera, G. A., and Haelig, A. W.: Clinical characteristics of hypertension associated with unilateral renal disease, Circulation 6: 549, 1952.

with unitateral renal disease, Circulation 6: 549, 1952.

8 Deming, Q. B.: Association of polyuria and albuminuria with hypertension of unilateral renal origin, Arch. Int. Med. 93: 197-204, 1954.

9 McDonald, R. T., Szilagyi, D. E., and Smith, R. F.: Nephrogenic hypertension (Goldblatt kidney) following operative trauma to the renal artery, Circulation-18: 71-75, 1958.

10 Shackelford, R. T., quoted by Howard et al., 11 p. 66.

11 Howard, J. E., Berthrong, B., Gould, D. M., and Yendt, E. R.: Hypertension resulting from unilateral renal vascular disease and its relief by nephrectomy, Bull. Johns Hopkins Hosp. 94: 51-85, 1954.

12 Pourtasse, E. F., and Dustan, H. P.: Arteriosclerosis and renal hypertension. Indi-

¹² Poutasse, E. F., and Dustan, H. P.: Arteriosclerosis and renal hypertension. Indications for aortography in hypertensive patients and results of surgical treatment of obstructive lesions of the renal artery, J. A. M. A. 165: 1521-1525, 1957.

13 Haller, J. A., Radigan, L. R., and Morrow, A. G.: Hypertension due to segmental infarction of the kidney, Am. J. Med. 22: 303-305, 1957.

do this, since the function of the good kidney may be temporarily reduced by the hypertension and be maintained 14 or improved 15 if a timely operation relieves the hypertension. A degree of ischemia which does not impair renal function as indicated by the usual tests may cause hypertension.

Pyelograms are sometimes helpful and should ordinarily be carried out. A smaller renal shadow on one side is important, especially if a shrinkage can be proved by comparison with a previous roentgenogram. A fainter shadow on one side in an intravenous pyelogram suggests reduced circulation or impaired tubular function on that side; and failure by intravenous pyelography to visualize the pelvis of a kidney which later yields a normal retrograde pyelogram strongly points to an obstruction of the renal artery. Normal pyelograms frequently occur, however, with serious unilateral disease.

Differential functional tests by means of bilateral ureteral catheterization offer more assistance. The relative amount of dyes excreted has not proved dependable, but Howard and his associates 11 found that a diminished volume of urine together with a lower concentration of sodium in the urine from one kidney, in specimens taken simultaneously, was highly significant. In a later report Howard 14 has confirmed these observations. He found that a reduction in volume of the urine of at least 50% and a reduction of sodium concentration of at least 15% from one kidney as compared with a specimen simultaneously obtained from the other indicated renal injury from ischemia and predicted a favorable outcome from nephrectomy. Of eight cases with satisfactory tests and subjected to nephrectomy, this test predicted the outcome accurately in all-successful in four, and without effect on the blood pressure in the other four.

Meticulous technic in performing the test is essential, however, and the authors enumerate many pitfalls which must be avoided, especially leakage of urine around a ureteral catheter. A diminution of sodium concentration on one side without information as to volume proved not dependable, and a diminished volume with equal or increased sodium concentration in the smaller specimen was not significant. Total lack of secretion by one kidney also does not indicate the nature of the renal lesion. Of 10 such cases subjected to nephrectomy in the hope they might be benefited, hypertension was relieved in eight, a better result than was anticipated or probably could ordinarily be expected.

Aortography if expertly performed is the most dependable single procedure for demonstrating arterial abnormalities. This is usually done by translumbar injection into the aorta at the level of the renals. The lower aorta, as well as the renal arteries and their principal branches can usually

 ¹⁴ Connor, T. B., Berthrong, M., Thomas, W. C., and Howard, J. E.: Hypertension due to unilateral renal disease—with a report on a functional test helpful in diagnosis, Bull. Johns Hopkins Hosp. 100: 241-276, 1957.
 ¹⁵ Imber, I., and Clymer, R. H.: Obstruction of the renal artery producing hypertension, New England J. Med. 252: 301, 1955.

be distinguished. Congenital anomalies such as aberrant vessels and circinate aneurysms can be distinguished but are rare. More frequent is partial or complete obstruction resulting from atherosclerotic plaque. Poutasse and Dustan ¹² have recently reported observations on 104 selected hypertensive subjects examined by aortography over a period of two years. Of these 30 showed focal renal arterial disease, in 23 atherosclerotic plaques (unilateral in 17), confirmed anatomically in 15. In six there was a post-stenotic aneurysmal dilatation of the vessel. Operation was carried out in 19, with two deaths; nephrectomy was performed in 14, arterial grafts or endarterectomy in four others. Of seven cases followed for over a year, the blood pressure was normal in five and two were much improved clinically. Of 10 cases followed less than a year, the pressure was normal in six and improvement was obtained in four. In three cases of pyelonephritis with contracted kidney, the renal vessels were contracted in the areas with parenchymal atrophy.

Aortography is an operative procedure which involves some risk, although this seems to be relatively slight. McAfee and Willson ¹⁶ reported one death and one case with renal injury requiring nephrectomy in 150 cases together with numerous minor disturbances. The chief danger seems to be from injection of an unduly large amount of concentrated solution directly into one renal artery, as in McAfee's case; more rarely into the mesenteric or coeliac axis, or into kidney tissue. This can usually be prevented by taking a preliminary plate after injecting a small amount of the material to check on the position of the needle.

A histologic study of the kidneys in cases successfully treated by nephrectomy has shown evidence of circulatory insufficiency. Howard 14 especially has stressed atrophy of the cortical parenchyma involving chiefly the tubules and largely sparing the glomeruli. This atrophy is often focal, but it may be widespread. He has described small tubular acini in the atrophic areas, with a small lumen lined by altered cuboidal but vital appearing cells which he regards as characteristic of "ischemic atrophy." This he contrasts with the dilated, "thyroid-like" tubules lined by flattened and presumably inactive cells which are typical of pyelonephritic atrophy. Acini of the ischemic type, which could conceivably be concerned in the secretion of a hypertensive agent, he found particularly along the margins of infarcted areas where the ischemia was marked but not severe enough to cause actual necrosis. In one case he found no renal changes although an aortogram had shown obstruction of the renal artery, a finding often noted in Goldblatt's hypertensive dogs. A biopsy offers little prospect of helping in diagnosis. The characteristic lesions are often localized in distribution and restricted in amount.

A striking feature is the usual absence of arteriolar changes in the ischemic kidney, whereas these develop, often rapidly, in the other kidney,

¹⁶ McAfee, J. G., and Willson, J. K. V.: A review of the complications of translumbar aortography, Am. J. Roentgenol. 75: 956-970, 1956.

in the retina and other organs generally. The ischemic kidney seems protected by its inadequate circulation from the hypertensive agent. There is usually fairly prompt and complete subsidence of such arteriolar changes, easily observed in the retina, if the hypertension can be terminated by timely treatment.

It is generally agreed that hypertension develops only if there is adequate ischemia but that there must be viable tubular tissue remaining. Complete infarction of one kidney does not cause hypertension. In most cases of localized renal infarction hypertension does not develop. As a rule there is a sharp demarcation between the infarcted area and healthy surviving tissue without an intermediate zone of atrophic but viable tubules.

In pyelonephritic kidneys, removal of which relieved the hypertension, Howard reported observing areas containing atrophic acini of the ischemic type, whereas in four cases showing only dilated thyroid-like acini with flattened cells (pyelonephritic type) no reduction in blood pressure was obtained. Kincaid-Smith 17 has also described atrophic acini of this type and evidence of vascular obstruction in cases of pyelonephritis who had had

hypertension.

In an effort to avoid fruitless major investigative procedures, especially aortography, Winters 18 has attempted to determine the vascularity of the kidneys by injecting intravenously Diodrast labeled with radioactive iodine. Continuous records of the gamma radiation are made over each kidney separately for 10 to 30 minutes. He described a preliminary peak coincident with the first flooding of the kidney and surrounding tissues with blood containing the contrast medium, and a second peak attributed to accumulation of Diodrast as it is removed from the blood by the tubules for excretion. Any notable diminution or delay in appearance is attributed to diminished vascularity or impaired tubular function. In 44 hypertensives examined, a unilateral abnormality was found in 10. Excretory urograms carried out in nine and aortograms in six were all "in harmony." The method seems to deserve further study as a possible screening measure, but at present it could not replace the more precise procedures where there is a reasonable suspicion of a unilateral vascular defect.

In a majority of the cases benefited by operation, nephrectomy has been carried out. Occasionally, however, reconstructive operations on the arteries have been successful. Thus Freeman et al.19 reported a case with claudication and hypertension who showed a thrombotic occlusion of the common iliacs and aorta up to and partly involving the left renal artery. He secured a virtual cure of these difficulties lasting at least two years by a thromboendarterectomy, pealing out the entire thrombus together with the adjacent

¹⁷ Kincaid-Smith, P.: Vascular obstruction in chronic pyelonephritic kidneys and its

Princial-Smith, P.: Vascular obstruction in chronic pyelonephritic kidneys and its relation to hypertension, Lancet 2: 1263, 1955.

18 Winters, C. C.: Unilateral renal disease and hypertension. Use of the radioactive Diodrast renogram as a screening test, J. Urol. 78: 107, 1957.

19 Freeman, N. E., Leeds, F. H., Elliott, W. G., and Roland, S. I.: Thromboendarterectomy for hypertension due to renal artery occlusion, J. A. M. A. 156: 1077, 1954.

superficial layers of the vessel. Some others have not been so successful in maintaining patency of the vessels after such an operation.

DeCamp 20 cured two cases by conservative operations on congenital arterial lesions, suturing the splenic artery to the left renal. Poutasse 21 cured one case by successive bilateral renal arterial grafts, and Winter 18 one case by resecting an area of coarctation of one renal artery and anastomosing the ends. The desirability of such constructive procedures is obvious when technically feasible and when the kidney has not already suffered excessive

permanent damage.

Selection of suitable cases for operation still presents great difficulties. There is no simple test, no short cut to determine this. A careful history will help select those who should have exhaustive examinations. At present most help is obtained from aortography and from differential functional studies as outlined by Howard. Successful results can not be anticipated from every case correctly diagnosed. Severe hypertension over too long a period will cause grave irreversible damage to the initially healthy kidney. How long this period is will vary greatly with the patient. It has been suggested that in an acute severe attack operation should be carried out in six weeks if spontaneous recovery has not occurred, as it occasionally does. On the other hand, in less fulminant cases, nephrectomy has been effective after two years and more of hypertension. Each case must be judged carefully and critically on the basis of all the facts available.

Although these cases form a small fraction of all hypertensive patients, they appear to be much commoner than those due to pheochromocytoma. They merit careful attention and careful study if there is a reasonable sus-

picion of the diagnosis.

PAUL W. CLOUGH, M.D.

20 DeCamp, P. T., and Birchall, R.: Recognition and treatment of renal arterial stenosis associated with hypertension, Surgery 43: 134-152, 1958.

21 Poutasse, E. F., Humphries, A. W., McCormack, L. J., and Corcoran, A. C.: Bilateral stenosis of renal arteries and hypertension, J. A. M. A. 161: 419, 1956.

REVIEWS

Carcinoma of the Lung. Volume I of Neoplastic Diseases at Various Sites. Edited by J. R. BIGNALL, M.D., M.R.C.P., Assistant Physician, Brompton Hospital, etc. General Editor: D. W. SMITHERS, M.D., F.R.C.P., F.F.R. 298 pages; 25.5 × 17.5 cm. E. & S. Livingstone Ltd., Edinburgh and London; The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. 1958. Price, \$10.50.

This volume is the first of a projected series of monographs on neoplastic disease at various sites under the general editorship of D. W. Smithers.

It is indeed appropriate that the first subject considered is cancer of the lung which is showing every sign of becoming the single worst killer of men in the prime of life.

The book is divided into five sections which consider (1) the mortality of the disease in England and Wales; (2) the causation of carcinoma of the lung; (3) its pathology; (4) its course; and (5) its treatment by surgery, radiotherapy, and chemotherapy.

The section on the present knowledge of the causation of carcinoma of the lung is written by Richard Doll who, with Horn, Hammond and Wynder, has participated in the important studies which have linked cigarette smoking with the disease. Dr. Doll brings out very well the grim point that the total male mortality would likely be no more than 10 to 20% of its present figure in the absence of smoking.

The section on pathology includes a discussion of Nohl's study in surgical material of the lymph node distribution of metastases from carcinoma of the various lobes.

Each of the sections is well written. The editor has covered the subject well in its most important aspects. Frequent and good use of illustrations has been made. The book should be of great interest and of help to those concerned with bronchogenic carcinoma, and is highly recommended as a knowledgeable treatise on the subject.

P. B. S.

Peripheral Circulation in Health and Disease. By Walter Redisch, M.D., F.A.C.P., and Francisco F. Tangco, M.D., B.S. 154 pages; 18 × 26 cm. Grune & Stratton, New York. 1957. Price, \$7.75.

Although there are many texts devoted to the peripheral vascular circulation in disease, this monograph serves a useful function primarily in organizing the material in a simple, easily readable fashion and in the inclusion of certain of the more recent advances in the field.

The text is divided into four major clinical sections. The first section considers the anatomic and physiologic aspects of the peripheral vascular system and the clinical methods of evaluating peripheral blood flow. The latter represents a valuable summary of the methods available to date. The second section considers, in brief clinical accounts, the major pathologic states that may alter peripheral blood flow. Section three is a short dissertation devoted to the development of collateral circulation. Section four concerns the therapy of peripheral vascular disorders, both from the medical and the surgical viewpoints. A bonus section is included, devoted largely to experimental observations bearing on newer concepts of circulation in muscular areas. This latter section will be of interest to the investigator in the field of peripheral circulation.

The major shortcoming of the monograph is in the brevity of the clinical material presented, so that for detailed information, other references must be consulted. Never-

theless, the text supplies an adequate bibliography and should be a valuable reference for the medical student and the practitioner of general medicine.

SHELDON E. GREISMAN, M.D.

Alcoholism: A Treatment Guide for General Practitioners. By Donald W. Hewitt, M.D. 112 pages; 14 × 20.5 cm. Lea & Febiger, Philadelphia. 1957. Price, \$3.00.

There are a number of startling facts about alcoholism that every physician should know. It is estimated that there are currently 4,712,000 Américans suffering from alcoholism. At least 1,650,000 problem drinkers are in industry. Alcoholism costs society in one single year more than one billion dollars. One out of every fifteen drinkers eventually becomes an alcoholic. For every alcoholic there are an additional four or five people who suffer—family, friends, employers, employees, etc. One out of every five alcoholics is a woman.

These facts are an indication of the seriousness of the problem of alcoholism, and point up the extreme importance for every physician to be acquainted with the problem, and to be familiar with treatment possibilities and limitations. Dr. Hewitt in his book has attempted to meet this need by describing in simple clear language

the current status of the problem of alcoholism.

Many physicians have tended to steer away from treating the alcoholic because of the troublesome, repeated relapses, and because of the apparent lack of coöperation obtained from the alcoholic. It is certainly futile to attempt to treat the alcoholic unless he is motivated, concerned about his problem, and eager to seek help. One of the basic difficulties here is the reluctance of the alcoholic to accept the diagnosis of alcoholism.

Two factors are essential in the establishment of the diagnosis of alcoholism. One is the loss of control over drinking exhibited by the alcoholic, and the other is the consequences of the alcoholic's recurrent drinking upon significant aspects of his life such as his economic adjustment, physical health, and interpersonal relations.

As Dr. Hewitt emphasizes, there are a variety of personality types encountered among alcoholics, and one must be sure that the patient is not basically psychotic

with symptomatic alcoholism.

With our present understanding of alcoholism, the only assured recommendation to the alcoholic and the only wise course open to him is complete and sustained abstinence. Most alcoholics come a cropper because of their repeated efforts and experiments in drinking in a controlled way, and regaining the social drinking once experienced by the alcoholic.

The author's chapters on the understanding of the alcoholic and advising the family are particularly valuable. Frequently it is necessary to treat the alcoholic's family and not just the alcoholic per se. The availability of literature on this topic in the home may at times make considerable difference in the accessibility of the

resistant alcoholic to accepting help.

I think the author does not give sufficient attention or credit to Alcoholics Anonymous as an important resource for certain alcoholics. It is true that there are alcoholics who do not relish certain aspects of the A.A. program, and it is also true that A.A. with its membership of 280,000 obviously reaches only a small fraction of the

total alcoholic group.

There are practical suggestions in Dr. Hewitt's book for the management of the acute alcoholic and the recommendation that hospitalization in a general hospital is feasible for those alcoholics who are coöperative, who have stopped drinking, who are suffering from withdrawal symptoms, and who want hospitalization during this crucial period. The use of intravenous fliuds, vitamins B and C, and the tranquilizing drugs is thoughtfully described. The all-important issue of follow-up therapy involv-

ing both individual conferences with the patient and the family and possible use of Antabuse and the conditioned reflex treatment comes in for appropriate attention.

The reviewer personally has little confidence in the rationale and efficacy of the the conditioned reflex treatment of the alcoholic whereas he feels that Antabuse can play an important role if combined with individual or group therapy. There is an increasing number of clinics for the treatment of the alcoholic where group therapy has been found to be an important adjunct in the total care of the alcoholic. The author has wisely stressed the importance of religion in the recovery of many alcoholics.

One point that the author neglects to mention is the likelihood of a dry drunk occurring after a period of sobriety. This is a time characterized by restlessness, irritability, some depression, and a strong urge to drink to alleviate these symptoms. Usually such periods, if weathered soberly, terminate within a period of several days to a week, and are followed by feelings of great relief and increased self-assurance. Patients frequently need to be alerted about this contingency and prepared to deal with it. Such episodes, as sobriety continues, become less frequent and less intense.

Alcoholism has often been described as a progressive illness. Recovery from alcoholism may similarly be a progressive state with gradual maturing capacity to

face stress soberly as a slowly achieved outcome.

The alcoholic needs to be honest with himself, to be sincere in his wish to achieve and maintain sobriety, to accept responsibility for his sobriety, and to accept the professional help he so sorely needs. He needs to know someone who has confidence that this can be done. He needs to learn that he does not have to drink. He needs to learn to accept his alcoholism as an illness about which he can do something, and not be full of resentment and despair that he is an alcoholic and try to deny his alcoholism by repeated, futile efforts to control drinking. In this undertaking, Dr. Hewitt is of great help to the general practitioner who is willing to undertake the important, urgent task of dealing with the alcoholics among his patients. The book is replete with valuable practical suggestions for the care and management of the alcoholic.

ISADORE TUERK, M.D.

Head Injuries: Mechanisms, Diagnosis and Management. By E. S. Gurdjian, M.D., and J. E. Webster, M.D. 482 pages; 16 × 24.5 cm. Little, Brown and Co., Boston. 1958. Price, \$14.00.

The authors, long recognized as authorities on trauma to the central and peripheral nervous systems, have reviewed material collected over a 25 year period, including data derived from 1285 cases of head injury, from 151 consecutively autopsied cases of head injury, and from a large collection of experimental material. They state that the bibliography was derived from some 2500 titles from the literature which they collected.

The clinical manifestations of various types of head injury are dealt with in one chapter, which is preceded by chapters treating anatomic considerations, mechanisms of head injury, and diagnostic technics. Detailed descriptions and appropriate illustrations clarify surgical technic and the care of patients with nonsurgical lesions. The special problems of head injuries in infants and children are outlined, as are the complications resulting from immediate and late effects of head injury. Special attention is given to head injuries resulting from athletic endeavors. In addition, there is a brief survey of the historic aspects and also a chapter dealing with medicolegal aspects of head injury.

This book should be of value to any practitioner whose duties include the management of head injuries, and this reviewer feels it will serve as a valuable reference source and practical guide for the surgical house officer.

W. H. M., JR.

Pathology for the Physician. 6th Ed. By WILLIAM BOYD, M.D., Dipl. Psychiat., M.R.C.P. (Edin.), Hon. F.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Can.), F.R.S. (Can.), LL.D. (Sask.), (Queen's), D.Sc. (Man.), M.D. (Oslo). 900 pages; 18.5 × 26.5 cm. Lea & Febiger, Philadelphia. 1958. Price, \$17.50.

This is a very extensive rewrite of "The Pathology of Internal Disease." In the preface Dr. Boyd states, "The re-writing has been done with the graduate rather than the undergraduate in mind, the physician or internist rather than the pathologist, the young rather than the old."

The book has a simple organization—it begins with Diseases of the Heart: "Of all the ailments which may blow out life's little candle, heart disease is the chief." It continues with the other organ systems, ending with The Internal Environment, which concludes: ". . . when all the natural frailties of our bodies are considered,

'Strange that a harp with so many strings Should stay in tune so long.'

Some object to Dr. Boyd's bent for whimsey; we consider it one of the great contributions to "Pathology for the Physician."

B. W. A.

Functional Localization In Relation to Frontal Lobotomy. By JOHN F. FULTON, O.B.E., M.D., D.Sc., LL.D. (Birm.). 140 pages; 13.5 × 21 cm. Oxford University Press, New York. 1949. Price, \$3.00.

This small volume contains four chapters which comprise the William Withering Memorial Lectures which were delivered by Dr. Fulton in 1948. The first chapter discusses the literature and experimentation concerned with the voluntary motor system. The second chapter discusses autonomic representation in the frontal lobes in subhuman primates and presents the experimental evidence regarding the relation of the frontal lobes to personality. The third chapter deals with frontal lobotomy in man. The fourth chapter discusses the newer (1948) experimental work delineating the functional organization of the cerebellum.

These lectures review the related literature prior to 1948 with a comprehensive bibliography appended to each chapter. Although this volume was most timely at the time of its publication almost ten years ago when frontal lobotomy was relatively new and less well evaluated than at present, perusal of these published lectures at this time will still be most rewarding to the reader. These lectures are of particular interest to those interested in neuroanatomy, neurophysiology, clinical neurology or neurosurgery.

C. V. B.

Clinical Heart Disease. 5th Ed. By SAMUEL A. LEVINE, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School. 673 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1958. Price, \$9.50.

The fifth edition of this stand-by of cardiology was necessitated by the recent advances in heart disease, particularly in the field of cardiac surgery, both for acquired and congenital heart disease. Advances in electrocardiography and the arrival of vectorcardiography likewise require attention. As implied, the emphasis is placed on clinical aspects of heart disease. The author has unusual ability to get at the core and important aspects of disease. There is a mature view of accomplishments and aims. It is most pleasant to have one's material lifted from the unnecessary gadgetry and formulae of today, though these are by no means spurned. The sections are divided into the usual etiological and functional categories. Of particular interest are the special sections on the clinical aspects of functional heart disease, cardiovascular emergencies, medicolegal aspects of disease and surgical and obstetrical risk. One, of course, will begin with the section on angina pectoris and coronary thrombosis and the sometimes controversial "chair" treatment following infarction and with congestive heart failure. Of necessity in a work of this type, the space allowed for some entities must be short, as with the rare forms of heart disease. There is a considerable section on congenital heart disease where the emphasis is placed on the clinical aspects; and a large section on electrocardiography. The section on vector-cardiography is concise and easily understood. All internists will find it a most worthwhile volume.

A. D. R.

Modern Perinatal Care. By Leslie D. Dill, M.D., F.A.C.S., Associate Clinical Professor of Obstetrics and Gynecology, Georgetown University School of Medicine. 309 pages; 16.5 × 24.5 cm. Appleton-Century-Crofts, Inc., New York. 1957. Price, \$6.50.

The contents of this volume fail to justify the title "Modern Perinatal Care." The term "modern" is satisfactory. Many aspects of perinatal (surrounding birth) care have been omitted. Intrapartal care was not considered at all; it appears obvious that only those problems of particular interest to the author have been included in antepartum and postpartum care. For example: hemorrhage is considered only in relationship to abortion; abruptio and placenta previa, cancer and polyp, etc. are not evaluated. In the puerperium the normal is reviewed and the abnormal omitted except for mastitis. This reviewer considers the volume to be one of either presenting too much (toxemia, heart disease, etc.) or too little (puerperal infection, thrombophlebitis, pyelitis, etc.).

The last three chapters in the volume justify publication. Here are considered medical records, civil law and the ethics of the Catholic church in relation to the practice of obstetrics. These subjects are treated not only adequately but well. There has been an urgent need for these discussions in a concise form and the author has done it admirably. These chapters should be a ready reference work for all

practicing obstetricians.

The book is published with inferior paper although the type is excellent. References are profuse at the end of each chapter. Illustrations are very sparse and are "original with the author and are not intended to present specific data but merely to give an approximate mean of assorted material."

The book has its main value and purpose in the chapters on medical records, legal aspects and the attitudes of the Catholic church towards obstetrics. For a

general reference work it is inadequate for antenatal and postnatal care.

D. FRANK KALTREIDER, M.D.

Electrocardiography. By MICHAEL BERNREITER, M.D., F.A.C.P. 134 pages; 18.5 × 23.5 cm. J. B. Lippincott Co., Philadelphia. 1958. Price, \$5.00.

There has been an increasing number of texts on electrocardiography published during the past several years. This is a reflection of the ever increasing interest in electrocardiography both as an effective clinical tool and as a means of basic investigation. In "Electrocardiography" the author attempts to cover the needs of the medical student, general practitioner, and internist. Unfortunately, many portions of the text are not lucidly presented. The section devoted to basic principles is not sufficient to furnish sound working concepts. It is hoped that future editions will remedy some of the errors in the legends and spelling. With the large number of texts now available, it is felt that there are others that cover the subject more adequately.

L. S.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- An Atlas of Esophageal Motility in Health and Disease. (This Atlas is from the Section of Physiology and the Section of Medicine, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.) By Charles F. Code, M.D., Ph.D., Professor of Physiology, Mayo Foundation, etc.; Brian Creamer, M.D., M.R.C.P. (London), Research Assistant, Section of Physiology, Mayo Clinic and Mayo Foundation; Jerry F. Schlegel, B.S., Technical Assistant, Section of Physiology, Mayo Clinic; Arthur M. Olsen, M.D., M.S. in Medicine, Associate Professor of Medicine, Mayo Foundation, etc.; F. Edmund Donoghue, M.D., M.S. in Medicine, Instructor in Medicine, Mayo Foundation, etc.; and Howard A. Andersen, M.D., M.S. in Medicine, Instructor in Medicine, Mayo Foundation, etc. 134 pages; 28.5 × 22 cm. 1958. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$8.50.
- Bewusstseinsverlust: Symptomatologie und dringliche Therapie. von Prof. Dr. Med. Habil. Wolfgang Hirsch und Dr. Med. Klaus Rust. 170 pages; 17.5 × 12.5 cm. 1958. VEG Georg Thieme, Leipzig. Price, geb. DM 9.30.
- Carcinoma of the Lung. Volume I of Neoplastic Disease at Various Sites. Edited by J. R. BIGNALL, M. D., M.R.C.P., Assistant Physician, Brompton Hospital, etc. General Editor: D. W. SMITHERS, M.D., F.R.C.P., F.F.R. 298 pages; 25.5 × 17.5 cm. 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents, Baltimore, Maryland. Price, \$10.50.
- The Care of the Geriatric Patient. Edited by E. V. COWDRY, Ph.D., Sc.D. (Hon.), Director of Wernse Cancer Research Laboratory, Washington University School of Medicine, etc. 438 pages; 20 × 13 cm. 1958. The C. V. Mosby Company, Saint Louis. Price, \$8.00.
- Cerebral Vascular Diseases: Transactions of the Second Conference Held under the Auspices of the American Heart Association, Princeton, New Jersey; January 16–18, 1957; Including a Classification and Outline of Cerebrovascular Diseases. A report by an ad hoc Committee established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, Public Health Service. IRVING S. WRIGHT, Chairman; CLARK H. MILLIKAN, Editor. 224 pages; 26 × 17.5 cm. 1958. Published for The American Heart Association by Grune & Stratton, New York. Price, \$4.00.
- Deficiency Disease: Functional and Structural Changes in Mammalia Which Result from Exogenous or Endogenous Lack of One or More Essential Nutrients. By RICHARD H. FOLLIS, JR., M.D. 577 pages; 26 × 18.5 cm. 1958. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$14.75.
- Electrocardiography. By Michael Bernreiter, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Kansas Medical School, etc. 134 pages; 23.5 × 18 cm. 1958. J. B. Lippincott Company, Philadelphia. Price, \$5.00.
- Enfermedades de los Conquistadores: Segundo Premio de Medicina, Certamen Nacional de Cultura, El Salvador, 1955. By Horacio Figueroa Marroquin. 228 pages; 20.5 × 15 cm. (paper-bound). 1957. Ministerio de Cultura, Departamento Editorial, San Salvador, El Salvador, C. A. Available from Librería Cultural Salvadoreña, S.A., 2a. Avenida Sur 19, San Salvador, El Salvador, C. A. Price, \$1.10.

- Guide to Russian Medical Literature. National Library of Medicine, Public Health Service Publication No. 602. Editors: Scott Adams, National Institutes of Health; and Frank B. Rogers, M.D., National Library of Medicine. 90 pages; 23 × 15 cm. (paper-bound). 1958. National Library of Medicine, Washington. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 40¢.
- Head Injuries: Mechanisms, Diagnosis and Management. By E. S. Gurdjian, M.D., Professor of Neurological Surgery and Chairman of the Department of Neurosurgery, Wayne State University College of Medicine, etc.; and J. E. Webster, M.D., Associate Professor of Neurological Surgery, Wayne State University College of Medicine, etc. 482 pages; 24.5 × 16 cm. 1958. Little, Brown and Company, Boston. Price, \$14.00.
- Heredity of the Blood Groups. By Alexander S. Wiener, A.B., M.D., F.A.C.P., F.C.A.P., Senior Bacteriologist (Serology) to the Office of the Chief Medical Examiner of New York City, etc.; and Irving B. Wexler, A.B., M.D., F.A.C.P., Associate Pediatrician, Jewish Hospital of Brooklyn, etc. 150 pages; 22.5 × 14 cm. 1958. Grune & Stratton, New York. Price, \$6.00.
- Leukämie im Kindesalter: Beiträge zur Morphologie, Klinik, Pathophysiologie und Therapie. von Dozent Dr. J. Oehme, Dr. W. Janssen and Dr. Ch. Hagitte. 169 pages; 24.5 × 17.5 cm. 1958. VEG Georg Thieme, Leipzig. Price, geb. DM 38.25.
- The Management of Emergencies in Thoracic Surgery. By John Borrie, M.B.E., Ch.M., F.R.C.S. (Eng.), F.R.A.C.S., Thoracic Surgeon, Dunedin Hospital and Southern Metropolitan Region, New Zealand, etc.; foreword by Sir Russell Brock. 340 pages; 25 × 17 cm. 1958. Appleton-Century-Crofts, Inc., New York. Price, \$10.00.
- Myasthenia Gravis. By KERMIT E. OSSERMAN, M.D., F.A.C.P., Physician-in-Charge, Myasthenia Gravis Clinic, The Mount Sinai Hospital, New York, etc. 286 pages; 23.5 × 15.5 cm. 1958. Grune & Stratton, Inc., New York. Price, \$10.00.
- Neurological Basis of Behaviour. Ciba Foundation Symposium in Commemoration of Sir Charles Sherrington, O.M., G.B.E., F.R.S., 1857-1952. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B.Sc. 400 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, \$9.00.
- The Nonoperative Aspects of Pediatric Surgery: Report of the Twenty-seventh Ross Pediatric Research Conference. 95 pages; 23 × 15 cm. (paper-bound). 1958. Ross Laboratories, Columbus, Ohio. Price: available on request.
- Obstetricia Social: Primer Premio de Medicina, Certamen Nacional de Cultura, El Salvador, 1955. By Cesar Emilio Lopez. 566 pages; 21 × 15 cm. (paper bound), 1957. Ministerio de Cultura, Departamento Editorial, San Salvador, El Salvador, C. A. Available from Libreria Cultural Salvadoreña, S.A., 2a. Avenida Sur 19, San Salvador, El Salvador, C. A. Price, \$2.00.
- The Organic Psychoses: A Guide to Diagnosis. By John G. Dewan, M.A., M.D., Ph.D. Cantab., D.P.M. Eng., F.R.C.P. (C), F.A.C.P., F.A.P.A., Associate Professor of Psychiatry, University of Toronto, etc.; and William B. Spaulding, M.D., F.R.C.P. (C), Associate Professor of Medicine, and Associate, Department of Phychiatry, University of Toronto, etc. 170 pages; 22.5 × 14.5 cm. 1958. University of Toronto Press, Toronto, Canada. Price, \$5.95.
- Pathophysiology in Surgery. By James D. Hardy, M.S. (Chem.), M.D., F.A.C.S., Professor and Chairman, Department of Surgery, and Director of Surgical Re-

- search, University of Mississippi Medical Center, etc. 704 pages; 26 × 18 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, \$19,00.
- Poisoning: A Guide to Clinical Diagnosis and Treatment. 2nd Ed. By W. F. von Oettingen, M.D., Ph.D., National Institutes of Health, U. S. Public Health Service, U. S. Department of Health, Education and Welfare. 627 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, \$12.50.
- The Public Looks at Hospitals. Health Information Foundation Research Series 4.

 By ELIOT FRIEDSON and JACOB J. FELDMAN. 25 pages; 23 × 15 cm. (paperbound). 1958. Health Information Foundation, New York. Price, available on request.
- Readings in Medical Care. Edited by the Committee on Medical Care Teaching of the Association of Teachers of Preventive Medicine. 708 pages; 24.5 × 16 cm. 1958. The University of North Carolina Press, Chapel Hill. Price, \$6.50.
- Schizophrenia. By Manfred Sakel. 335 pages; 21.5 × 14 cm. 1958. Philosophical Library, New York, Price, \$5.00.
- El Servicio de Maternidad en el Hospital Rosales: Compendio de sus Labores Obstétricas en el Curso de 34 Años. By Cesar Emilio Lopez. 628 pages; 25 × 17.5 cm. (paper-bound). 1955. Ministerio de Cultura, Departamento Editorial, San Salvador, El Salvador, C. A. Available from Librería Cultural Salvadoreña, S.A., 2a Avenida Sur 19, San Salvador, El Salvador, C. A. Price, \$2.40.
- Tetanie, von Doz. Dr. Hans Jesserer. 191 pages; 24 × 17 cm. (paper-bound). 1958. Georg Thieme Vérlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York, N. Y.
- Treatment of Breast Tumors. By ROBERT S. POLLACK, M.D., F.A.C.S., Clinical Instructor in Surgery, Stanford University School of Medicine, etc. 147 pages; 26.5 × 18 cm, 1958, Lea & Febiger, Philadelphia. Price, \$6.00.
- Tumors and Tumorous Conditions of the Bones and Joints. By Henry L. Jaffe, M.D., Director of Laboratories and Pathologist, Hospital for Joint Diseases, New York, N. Y., etc. 629 pages; 26.5 × 18 cm. 1958. Lea & Febiger, Philadelphia. Price, \$18.50.
- Urology in General Practice. By Frank Coleman Hamm, M.D., M.S., F.A.C.S., Professor of Urology, Department of Surgery, State University of New York Downstate Medical Center, etc.; and Sidney R. Weinberg, M.D., F.A.C.S., Assistant Professor of Urology, Department of Surgery, State University of New York Downstate Medical Center, etc.; illustrated by Elizabeth Cuzzort. 293 pages; 28 × 21.5 cm. (paper-bound). 1958. J. B. Lippincott Company, Philadelphia. Price, \$6.00.
- Water and Electrolyte Metabolism in Relation to Age and Sex. Volume 4 of the Ciba Foundation Colloquia on Ageing. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. 327 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, \$8.50.
- What We DO Know About Heart Attacks. By John W. Gofman, M.D., Professor of Medical Physics, University of California, Berkeley. 180 pages; 21 × 14 cm. 1958. G. P. Putnam's Sons, New York. Price, \$3.50.

COLLEGE NEWS NOTES

BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

Walter L. Bierring, M.D., M.A.C.P., Des Moines, Iowa, A HISTORY OF THE DEPARTMENT OF INTERNAL MEDICINE—STATE UNIVERSITY OF IOWA COLLEGE OF MEDICINE—1870-1958, published by the State University of Iowa, Iowa City, 1958, 116 pages.

Edward A. Strecker, M.D., F.A.C.P., and Kenneth E. Appel, M.D., F.A.C.P., Philadelphia, Pa., DISCOVERING OURSELVES, published by the Macmillan Com-

pany, New York, N. Y., 1958, 303 pages.

Edwin P. Jordan, M.D., F.A.C.P., Charlottesville, Va., THE PHYSICIAN AND GROUP PRACTICE, published by The Year Book Publishers, Inc., Chicago, Ill., 1958, 238 pages.

A.C.P. DIRECTORY SUPPLEMENT, 1958

The last complete Directory of the American College of Physicians was published in the autumn of 1955. A Supplement thereto was published in the autumn of 1956 and one in 1957. This 1958 Supplement includes all alterations and additions to the 1955 Directory since its publication.

A free copy of the 1958 Supplement will be sent, on request, to any member of the College who purchased a 1955 Directory, or to any Medical School or Library

which already has a copy of the 1955 Directory.

A free copy of the 1958 Supplement has already been sent automatically to Life Members and to Deans of Medical Schools in the United States and Canada.

The Supplement is available at \$2.50 per copy, postpaid, to all others.

College Names New U. S. AIR FORCE GOVERNOR

Major General Oliver K. Niess, F.A.C.P., recently appointed Surgeon General of the U. S. Air Force, was named a Governor of the College for the U. S. Air Force at the November 15 meeting of the Board of Regents of the College. General Niess was named Air Force Surgeon General on December 1, 1958, replacing Major General Dan C. Ogle, former Air Force Surgeon General who retired November 30, 1958.

General Niess had served as Command Surgeon of the Pacific Air Forces in Hawaii, a position which he held since September, 1954. He organized and supervised the Pacific Air Force Medical Conference which is attended by representatives of the Asiatic countries and has been instrumental in establishing medical care for U. S. nationals throughout southeast Asia. During World War II, he served as: Director of Administration in the Office of the Air Surgeon, Washington, D. C.; as Surgeon of the India-China Division, Air Transport Command, Calcutta, India, and as Surgeon of the Pacific Division, Air Transport Command, in Hawaii.

General Niess is a graduate of the Army Medical Service School of the U. S. Air Force School of Aviation Medicine, and the Command and General Staff School. He is board certified in aviation medicine and is rated as Chief Flight Surgeon and as Aircraft Observer (Medical). He is a Fellow of the American College of Surgeons; a member of the American Medical Association, and the Association of Mili-

tary Surgeons.

A.C.P. REGIONAL MEETINGS

Atlantic Provinces, November 7-8; New Jersey, November 12; North Carolina, December 4; Puerto Rico, December 19-20; Colorado, January 16-17; Ohio, January 22, and Eastern Pennsylvania, January 23. The following regional meetings have been held during the past months: North Dakota, September 6; Michigan, September 19-20; Idaho-Utah, September 27; Midwest (III., Ind., Iowa, Minn., Wis.), September 27; Western New York, October 3; Southeastern (Ala., Fla., Ga., Miss., S. C., Cuba), October 3-4; Montana-Wyoming. October 10-11; Arizona, October 18; Arkansas-Oklahoma, October 18; Kentucky-Tennessee, October 18; District of Columbia-Maryland, November 1; New England-Quebec-

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Official Guest(s)	Fuller B. Bailey, Regent	Dwight L. Wilbur, Pres. Howard P. Lewis, PresElect	Howard P. Lewis, PresElect		Dwight L. Wilbur, Pres.	Dwight L. Wilbur, Pres.		Dwight L. Wilbur, Pres.
. Governor(s)	Percy H. Sprague Francis A. L. Mathewson	George C. Griffith	H. A. Des Brisay M. L. Margason J. W. Haviland	Marion D. Hargrove Laurance J. Clark, Sr.	Carl V. Moore	Edmond M. Walsh	Fred J. McEwen	Charles M. Caravati
Date	January 29, 1959	February 7-8, 1959 George C. Griffith	Vancouver, B. C., February 14, 1959 Canada	February 20, 1959	February 21, 1959	March 7, 1959	March 20, 1959	March 21, 1959
City	Banff, Alberta, Canada	Palm Springs	Vancouver, B. C., Canada	Jackson, Miss.	Kansas City	Omaha	Wichita	Hot Springs
Territory	Alberta, Manitoba and Saskatchewan, Canada	Southern California	Pacific Northwest (British Columbia, Oregon, Washington)	Louisiana, Mississippi	Missouri	Nebraska	Kansas	Virginia

MAJOR GENERAL DAN C. OGLE, F.A.C.P., AIR FORCE SURGEON GENERAL RETIRES

After almost 30 years of active service, Major General Dan C. Ogle, F.A.C.P., Air Force Surgeon General, Washington, D. C., and former A.C.P. Governor for the U. S. Air Force, retired on November 30, 1958.

A Chief Flight Surgeon since 1932, General Ogle has dedicated himself to aeromedicine in its broadest aspects. Under his administration the Air Force has developed an Aeromedical Research Center at Brooks Air Force Base, Tex., and has constructed 170 new medical facilities throughout the world. In March 1953, General Ogle was named Surgeon of the U. S. Air Force in Europe at Wiesbaden, Germany, and a year later was called to Washington to assume the position of Air Force Surgeon General.

He is a Fellow of the Aero Medical Association; an Honorary Fellow of the International College of Surgeons, the Southeastern Surgical Congress, the American College of Chest Physicians, and the American Association for the Surgery of Trauma; a Diplomate of the American Board of Preventive Medicine with certification in Aviation Medicine (Founders Group); Honorary Director of the American Foundation for Tropical Medicine; Advisory Vice President of the Pan-American Medical Association; a Selector of the International Academy of Aviation Medicine; a member of the National Board of Medical Examiners, the American Medical Association, the Association of Military Surgeons, the Advisory Board for Prevention of Asphyxial Death, the Gorgas Memorial Institute of Tropical and Preventive Medicine, the Advisory Editorial Board for the Journal of Aviation Medicine, and the Board of Regents of the National Library of Medicine.

RESIDENCY IN PULMONARY DISEASES AVAILABLE

A residency at the Baylor University College of Medicine, Houston, Tex., is available immediately. It provides an opportunity for training in endoscopy, pulmonary physiology, tuberculosis and non-tuberculous diseases of the chest. Candidates should have one or more years' residency in internal medicine. Address inquiries to Daniel E. Jenkins, M.D., Department of Medicine, Baylor University College of Medicine, Houston, Tex.

PEDIATRIC FELLOWSHIPS

Eighteen fellowships are available to pediatric residents for the fiscal year 1959-60 under grants to be made by the American Academy of Pediatrics. The fellowships which include a period of six months to one year, have been created to provide help for young physicians who are residents of the United States or Canada and who are in need of financial assistance to complete their pediatric training. The stipends range from \$500 to \$1,000, beginning July 1, 1959. Address inquiries to the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

CHILD PSYCHIATRY TRAINEESHIPS

Two traineeships in child psychiatry are available at the Walter E. Fernald State School, Waverly, Mass., under the direction of the Training and Standards Branch, National Institute of Mental Health, Bethesda, Md. The program is intended for physicians who wish to complete their psychiatric training by spending a year in a school for the mentally retarded. Inquiries should be addressed to Dr. Clemens E. Benda, Director of Psychiatry and Research, Walter E. Fernald State School, Box C, Waverly 78, Mass.

CARIBBEAN POSTGRADUATE CRUISE

The second medical cruise to the Caribbean sponsored by the University of Texas Postgraduate School of Medicine, Houston, Tex., will be conducted May 5-18, 1959. Twenty-five hours of teaching will be included in the fields of medicine, radiology, surgery, obstetrics and gynecology, and pediatrics. For information write The University of Texas, Postgraduate School of Medicine, Houston 25, Tex.

POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the Fourth Annual Postgraduate Course on Diseases of the Chest at the Sir Francis Drake Hotel, San Francisco, Calif., February 16–20, 1959. The most recent advances in the diagnosis and treatment of heart and lung diseases, medical and surgical aspects, will be presented. Tuition for this five-day course will be \$100. Further information may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, III.

CERTIFYING BOARD EXAMINATIONS

American Board of Internal Medicine—William A. Werrell, M.D., Executive Secretary-Treasurer, 1 West Main St., Madison, Wis. Oral examinations, February 3-6, 1959, New Orleans, La.; April 15-18, 1959, Chicago, Ill.; September 9-12, 1959, Portland, Ore., and November 6-7 and 9-10, 1959, Boston, Mass. Sub-Specialty Examination—Gastroenterology: April 17-18, 1959, Philadelphia, Pa.

The American Board of Physical Medicine and Rehabilitation—Earl C. Elkins, M.D., Secretary, 200 1st St., S.W., Rochester, Minn. Examination, June 12-13, 1959, Philadelphia, Pa. Applications must be in by February 15, 1959.

The American Board of Preventive Medicine—Tom F. Whayne, M.D., Assistant Secretary-Treasurer, University of Pennsylvania, Philadelphia 4, Pa. Aviation Medicine, April 24-26, 1959, Los Angeles, Calif. Occupational Medicine, April 17-19, 1959, Chicago, Ill. Public Health, April 9-11, 1959, regional basis at the various schools of Public Health. Applications must be in 90 days prior to the examination.

American Board of Psychiatry and Neurology—David A. Boyd, Jr., M.D. Secretary-Treasurer, 102-110 2nd Ave., S.W., Rochester, Minn. Examination, March 16-17, 1959, New Orleans, La.

The American Board of Radiology—H. Dabney Kerr, M.D., Secretary, Kohler Hotel Bldg., Rochester, Minn. Special examination, March 16-19, 1959, Cincinnati, Ohio.

1959 Schedule of American Meetings-February to June

- AMERICAN ACADEMY OF ALLERGY, Chicago, Ill., February 9-11. Dr. Bram Rose, Secretary, Royal Victoria Hospital, Montreal, Quebec, Can.
- AMERICAN ACADEMY OF FORENSIC SCIENCES, Chicago, Ill., February 26-28. Dr. Walter J. R. Camp, Secretary, 1853 W. Polk St., Chicago 12, Ill.
- AMERICAN ACADEMY OF OCCUPATIONAL MEDICINE, Boston, Mass., February 11-13. Dr. L. Blaney, Secretary, 1608 Walnut St., Philadelphia 3, Pa.
- AMERICAN COLLEGE OF RADIOLOGY, Chicago, Ill., February 6-7. Mr. William C. Stronach, Executive Director, 20 N. Wacker Dr., Chicago 6, Ill.

- AMERICAN COLLEGE OF ALLERGISTS, San Francisco, Calif., March 15-20. Dr. M. Coleman Harris, Secretary, 450 Sutter St., San Francisco, Calif.
- NATIONAL HEALTH COUNCIL, Chicago, Ill., March 17-19. Mr. Philip E. Ryan, Executive Director, 1790 Broadway, New York 19, N. Y.
- NATIONAL MULTIPLE SCLEROSIS SOCIETY, New York, N. Y., March 9. Mr. Donald Vail, Secretary, 257 4th Ave., New York 10, N. Y.
- AERO MEDICAL ASSOCIATION, Los Angeles, Calif., April 27-29. Dr. Thomas H. Sutherland, Secretary, P. O. Box 26, Marion, Ohio
- AMERICAN ASSOCIATION OF ANATOMISTS, Seattle, Wash., April 1-3. Dr. B. Flexner, Secretary, University of Pennsylvania School of Medicine, Philadelphia, Pa.
- AMERICAN ACADEMY OF NEUROLOGY, Los Angeles, Calif., April 13-18. Dr. Joseph M. Foley, Secretary, Boston City Hospital, Boston, Mass.
- AMERICAN ASSOCIATION OF IMMUNOLOGISTS, Atlantic City, N. J., April 13-17. Dr. Calderon Howe, Secretary, 630 W. 168th St., New York 32, N. Y.
- AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLO-GISTS, Boston, Mass., April 23-25. Dr. Russell L. Holman, Secretary, 1542 Tulane Ave., New Orleans 12, La.
- AMERICAN ASSOCIATION FOR THE STUDY OF NEOPLASTIC DIS-EASES, Gatlinburg, Tenn., April 30-May 4. Dr. Bruce H. Sisler, Secretary, Box 268, Gatlinburg, Tenn.
- AMERICAN COLLEGE OF PHYSICIANS, Chicago, Ill., April 20-24. Mr. E. R. Loveland, Executive Secretary, 4200 Pine St., Philadelphia 4, Pa.
- AMERICAN GOITER ASSOCIATION, Chicago, Ill., April 30-May 2. Dr. John C. McClintock, Secretary, 1491/2 Washington Ave., Albany, N. Y.
- AMERICAN PHYSIOLOGICAL SOCIETY, Atlantic City, N. J., April 12-16.
 Dr. Ray G. Daggs, Executive Secretary, 9650 Wisconsin Ave., Washington, D. C.
- AMERICAN PSYCHIATRIC ASSOCIATION, Philadelphia, Pa., April 27-May
 1. Dr. C. H. Hardin Branch, Secretary, 156 Westminster Ave., Salt Lake City,
 Utah
- AMERICAN RADIUM SOCIETY, Hot Springs, Va., April 6-8. Dr. Robert L. Brown, Secretary, Robert Winship Clinic, Emory University, Atlanta 22, Ga.
- AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY, Atlantic City, N. J., April 13-18. Dr. J. F. A. McManus, Secretary, University of Alabama Medical Center, Birmingham 3, Ala.
- AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, Atlantic City, N. J., April 13-17. Dr. Harold Hodge, Secretary, University of Rochester, Rochester 20, N. Y.
- AMERICAN SOCIETY FOR THE STUDY OF STERILITY, Atlantic City, N. J., April 3-5. Dr. Herbert H. Thomas, Secretary, 920 S. 19th St., Birmingham 5, Ala.
- INDUSTRIAL MEDICAL ASSOCIATION, Chicago, Ill., April 26-29. Dr. Leonard Arling, Secretary, 3101 University Ave., S. E., Minneapolis 14, Minn.
- AMERICAN ASSOCIATION FOR THE HISTORY OF MEDICINE, Cleveland, Ohio, May 21-23. Dr. John B. Blake, Secretary, Smithsonian Institution, Washington 25, D. C.

- AMERICAN COLLEGE OF CARDIOLOGY, Philadelphia, Pa., May 26-29. Dr. Philip Reichert, Secretary, 480 Park Ave., New York 22, N. Y.
- AMERICAN PEDIATRIC SOCIETY, Buck Hill Falls, Pa., May 6-8. Dr. A. C. McGuinness, Secretary, 2800 Quebec St., Washington 8, D. C.
- AMERICAN PSYCHOSOMATIC SOCIETY, Atlantic City, N. J., May 2-3. Dr. Morton F. Reiser, Secretary, 265 Nassau Rd., Roosevelt, N. Y.
- AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Atlantic City, N. J., May 3-4. Dr. S. J. Farber, Secretary, 550 1st Ave., New York 16, N. Y.
- AMERICAN TRUDEAU SOCIETY, Chicago, Ill., May 25-27. Dr. E. P. K. Fenger, Secretary, 1790 Broadway, New York 19, N. Y.
- ASSOCIATION OF AMERICAN PHYSICIANS, Atlantic City, N. J., May 5-6. Dr. Paul B. Beeson, Secretary, Yale University School of Medicine, New Haven 11, Conn.
- SOCIETY OF AMERICAN BACTERIOLOGISTS, St. Louis, Mo., May 10-15. Dr. E. M. Foster, Secretary, University of Wisconsin, Madison 6, Wis.
- SOCIETY FOR PEDIATRIC RESEARCH, Buck Hill Falls, Pa., May 8-9. Dr. Clark D. West, Secretary, Children's Hospital, Cincinnati 29, Ohio
- AMERICAN ACADEMY OF TUBERCULOSIS PHYSICIANS, Atlantic City, N. J., June 6. Dr. Oscar S. Levin, Secretary, P. O. Box 7011, Denver 6, Colo.
- AMERICAN COLLEGE OF CHEST PHYSICIANS, Atlantic City, N. J., June 3-7. Mr. Murray Kornfeld, Executive Director, 112 E. Chestnut St., Chicago 11, Ill.
- AMERICAN DERMATOLOGICAL ASSOCIATION, Atlantic City, N. J., June 1-4. Dr. Wiley M. Sams, Secretary, 25 Southeast 2nd Ave., Miami, Fla.
- AMERICAN DIABETES ASSOCIATION, Atlantic City, N. J., June 6-7. Dr. E. Paul Sheridan, Secretary, 1 E. 45th St., New York 17, N. Y.
- AMERICAN GERIATRICS SOCIETY, Atlantic City, N. J., June 4-5. Dr. Richard J. Kraemer, Secretary, 2907 Post Rd., Warwick, R. I.
- AMERICAN NEUROLOGICAL ASSOCIATION, Atlantic City, N. J., June 15-17. Dr. Charles Rupp, Secretary, 133 S. 36th St., Philadelphia 4, Pa.
- AMERICAN RHEUMATISM ASSOCIATION, Washington, D. C., June 2-6. Dr. Edward F. Hartung, Secretary, 580 Park Ave., New York 21, N. Y.
- SOCIETY OF BIOLOGICAL PSYCHIATRY, Atlantic City, N. J., June 13-14. Dr. George N. Thompson, Secretary, 2010 Wilshire Blvd., Los Angeles 57, Calif.
- THE ENDOCRINE SOCIETY, Atlantic City, N. J., June 4-6. Dr. Henry T. Turner, Secretary, 1200 N. Walker St., Oklahoma City 3, Okla.

ANNOUNCE INFORMATION SERVICE FOR PHYSICIANS IN SOUTHEAST

Dr. William M. Nicholson, F.A.C.P., Director of Postgraduate Medical Education at Duke University Medical Center, Durham, N. C., recently announced the development of an information service for physicians in the states of North and South Carolina and Virginia. The monthly booklet will be entitled WHAT GOES ON and will list all medical meetings, postgraduate courses, and other medical events in the three states. Distribution will be financed by the Lederle Laboratories Division of the American Cyanamid Company. Similar WHAT GOES ON publications are available for physicians in New England, New York and Texas under Lederle sponsorship.

NUTRITION EDUCATION PROGRAMS IN THE STATE OF PENNSYLVANIA

The Commission on Nutrition of the State of Pennsylvania, under the Chairman-ship of Dr. Michael G. Wohl, F.A.C.P., Philadelphia, Pa., in coöperation with the National Vitamin Foundation, has undertaken a program of nutrition education among practicing physicians throughout the state. The program is intended to: (1) stimulate interest in clinical nutrition at state and county levels; and (2) disseminate factual information on nutrition to the practicing physicians and the laity. Monthly meetings have been held throughout the state. The last one was held at Atlantic City, N. J., for the New Jersey Academy of General Practice on January 10, 1959.

ANNUAL MEETING OF THE OHIO SOCIETY OF INTERNAL MEDICINE

The Annual Meeting of the Ohio Society of Internal Medicine was held Wednesday, January 21, 1959, at Cincinnati, Ohio. The presiding officers were Dr. Arnoldus Goudsmit, Youngstown, Ohio, President; Dr. George J. Hamwi, F.A.C.P., Ohio State University College of Medicine, Columbus, Ohio, Vice President, and Dr. Leonard P. Caccamo, (Associate), Youngstown, Ohio, Secretary-Treasurer. The Annual Meeting was devoted to: a review of the progress made by the Society in the interest of patient care requiring the specialty of Internal Medicine in the State of Ohio during the year 1958; plans for the activities for the coming year; report by a special liaison committee with the Ohio Medical Indemnity, Inc., and a change of the by-laws of the organization. Dr. Arnoldus Goudsmit delivered the presidential address.

Dr. A. Carlton Ernstene, F.A.C.P., Governor of the College for Ohio, invited the Ohio Society of Internal Medicine to take part in the program of the Ohio Regional Meeting of the American College of Physicians. The Society planned a part of the program, which included the presentation of a panel dealing with the subject, "Status of the Internist in Medical Care Plans." Moderator of the panel was Dr. George J. Hamwi, F.A.C.P. The panel consisted of: Dr. William B. Walsh, (Associate), Chairman of the Legislative Committee of the American Society of Internal Medicine, Washington, D. C.; Dr. John J. Grady, F.A.C.P., Chairman of the Committee on Insurance Plans of the Cleveland Society of Internal Medicine, Cleveland, Ohio; Mr. Charles H. Coghlan, Executive Vice President of the Ohio Medical Indemnity, Inc., Columbus, Ohio and Dr. Paul I. Robinson, F.A.C.P., Coordinator of Medical Relations for the Metropolitan Life Insurance Company, representing the Health Insurance Council, New York, N. Y.

SECOND PAN-AMERICAN CONGRESS ON RHEUMATIC DISEASES

The Second Pan-American Congress on Rheumatic Diseases under the auspices of the Pan-American League Against Rheumatism and organized by the Pan-American Committee of the American Rheumatism Association, will be held June 2-6, 1959, at Washington, D. C., and Bethesda, Md. Dr. Richard H. Freyberg, F.A.C.P., New York, N. Y., is President of the Pan-American Committee of the American Rheumatism Association. Drs. Joseph L. Hollander, F.A.C.P., Philadelphia, Pa., and Robert M. Stecher, F.A.C.P., Cleveland, Ohio, are serving on the Committee. Titles and abstracts for submission of scientific papers to be considered by the Program Committee for presentation at the Congress should be submitted before February 1, 1959. Abstracts should be limited to 300 words and ten copies are required. Send to Dr. John Vaughan, University of Rochester School of Medicine, 260 Crittenden Blvd., Rochester, N. Y. Registration for the Congress is \$15.00 for all individuals. Applications should be sent to Dr. Richard T. Smith, West Point, Pa., before March 1, 1959.

WORLD MEDICAL ASSOCIATION ANNOUNCES 1959 MEETINGS

The World Medical Association announces the following schedule of meetings: 35th Council Session, Sydney, Australia, March 25-April 4, 1959; Second World Conference on Medical Education, Chicago, Ill., August 30-September 4, 1959; 13th General Assembly, Montreal, Canada, September 7-12, 1959. For information write: The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

SIXTH INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

The Sixth International Congress of Internal Medicine will be held in Basel, Switzerland on August 24–27, 1960. It will be sponsored by the International Society of Internal Medicine. Professor Doctor A. Gigon, former President of the Society, will serve as President of the Sixth Congress. Over 2,000 physicians in the United States, its possessions and Canada are members of the Society. Many of these attended the Fifth Congress which was held in Philadelphia, Pa., on April 24–26, 1958. For information write Prof. Dr. A. Gigon, 13 Petersplatz, Basel, Switzerland.

AERO MEDICAL ASSOCIATION MEETING

The 30th Annual Meeting of the Aero Medical Association will be held at the Statler Hotel in Los Angeles, Calif., April 27-29, 1959. For information write Charles I. Barron, M.D., General Chairman, Lockheed Aircraft Corporation, 2555 N. Hollywood Way, Burbank, Calif.

Two Retirement Organizations Announce New Publications

The American Association of Retired Persons, a national non-profit organization, has announced the publication of a new magazine entitled MODERN MATURITY. It has been developed as a part of the objectives of the Association which are to help spread the achievement of high-level well-being among older persons, of recognizing their economic needs and attempting to meet them. It attempts to explore the challenges offered the individual, not only for the satisfying betterment of his own place in society, but also for his responsibility for the society of which he could be a helpful and constructive member. For information, write the American Association of Retired Persons, 310 E. Grand Ave., Ojai, Calif.

The Emeriti Census has recently released its first newsletter entitled THE EMERITUS. The Emeriti Census has been organized for the following purposes: 1. To assist retired college and university professors and administrators to find greater security, especially through their own efforts to become reëmployed and self-sufficient; 2, To aid American institutions of higher education, that are faced by manpower shortage, to find additional mature, experienced research or teaching personnel during a critical national emergency; 3. To further the research and the publications of Emeriti members by helping them to secure fellowships and grants-in-aid; 4. To counsel in the improvement of academic retirement systems, many of which are made inadequate by the inflation; 5. To give advice on meeting the housing needs of Emeriti; 6. To increase the well-being of Emeriti by helping them to secure group insurance; 7. To find ways to lessen the distress of academic widows and other survivors. For information, write THE EMERITUS, P. O. Box 24451, Los Angeles 24, Calif.

PERSONAL NOTES

Dr. E. Gray Dimond, F.A.C.P., Kansas City, Kans., discussed the subject, "Exercise Electrocardiogram as an Office Procedure," at the Annual Scientific Session of the Oregon Academy of General Practice at Portland, Ore., October 16-17, 1958.

Dr. George F. Evans, F.A.C.P., Clarksburg, W. Va., was named President of the West Virginia State Medical Association at the Annual Meeting of the Association at The Greenbrier, August 21–23, 1958.

Captain Herbert G. Shepler, (Associate), (MC) U. S. Navy, Director, Aviation Medical Acceleration Laboratory, Johnsville, Pa., is experimenting with the only facilities in the world for simulating actual flight patterns of an aircraft. Using a large human centrifuge coupled with an analog computer, test pilots fly through actual flight patterns of the X-15 research aircraft.

Dr. Henry A. Arkless, (Associate), was promoted recently to the position of Chief of Medicine at the Woman's Hospital of Philadelphia, Pa.

Dr. Ralph W. Mays, F.A.C.P., was appointed Associate Professor of Medicine, and Drs. Wallace G. McCune, (Associate), and W. Lawrence Cahall, F.A.C.P., were named Assistant Professors of Medicine at the Jefferson Medical College of Philadelphia, Pa.

Dr. Harry Shubin, (Associate), Philadelphia, Pa., lectured during the Summer on the subject, "Steroids and Pulmonary Disease," at the following foreign medical institutions: Sanatorium Sotiria, Athens, Greece; Patel Chest Institute and University of Delhi, Delhi, India; University of Lucknow, Lucknow, India, and the Medical Society of Thailand in Bangkok. At the 5th International Chest Congress in Tokyo, Japan, he served as Chairman of the International Committee on Non-Surgical Therapy in Pulmonary Diseases and presented an exhibit and paper on "Steroid Therapy and Tuberculosis."

Dr. Harold C. Ochsner, Sr., F.A.C.P., Indianapolis, Ind., was named a Delegate to the American Medical Association from the Indiana State Medical Association at the October meeting of the latter organization.

Dr. Maurice S. Segal, F.A.C.P., Boston, Mass., presented the following papers recently: "Pulmonary Aspects in Management of Chronic Dyspneic Diseases," Postgraduate Course, Roger Williams Hospital, Providence, R. I., September 17; "X-Ray Workshop," General Electric Company Physicians, Boston City Hospital, October 2; "Pressure Breathing Therapy in Diseases of the Chest," Illinois Chapter of the American College of Chest Physicians, Chicago, Ill., October 15; "Clinical Cardiopulmonary Physiology," Postgraduate Course, American College of Chest Physicians, Chicago, Ill., October 16; "Diagnosis and Management of Pulmonary Emphysema in the Older Age Group," Medical Society of the County of Queens, Forest Hills, N. Y., October

28, and "Bronchial Asthma," Eastern Section, American Trudeau Society, Boston, Mass., October 31.

Dr. Edward G. Billings, F.A.C.P., Denver, Colo., gave the Presidential Address at the 34th Annual Meeting of the Central Neuropsychiatric Association held in Columbus, Ohio, October 17–18, 1958.

Three Fellows of the College were participants at the Mississippi Valley Conference on Tuberculosis held in Dayton, Ohio, October 15–18, 1958. Drs. William M. Spear, Oakdale, Iowa, and Harold G. Curtis, Cleveland, Ohio, presided at two scientific sessions and Dr. Virgil A. Plessinger, Cincinnati, Ohio, moderated a panel discussion on "Inoperable Pulmonary Neoplasm."

Dr. Walter H. Baer, F.A.C.P., Peoria, Ill., and Dr. Leo H. Bartemeier, F.A.C.P., Baltimore, Md., presided at the discussion sessions at the 5th Annual Conference of Mental Health Representatives of the State Medical Associations held in Chicago, Ill., November 21, 1958.

Dr. Harold L. Israel, F.A.C.P., Philadelphia, Pa., spoke on the subject, "Current Knowledge and Control of Beryllium Disease," at the Massachusetts Institute of Technology, Cambridge, Mass., September 30, 1958.

Two Fellows and two Associates of the College participated in the 30th Annual Conference of the American Association of Medical Record Librarians held in Boston, Mass., October 13–16, 1958. The Fellows were Drs. Henry Baker, Clinical Professor of Medicine, Tufts University School of Medicine and Dr. Morton G. Brown, Chief of Professional Service, Lemuel Shattuck Hospital, Boston, Mass. The Associates were Dr. Elmer E. Hinton, Chief of Medical Services, Cambridge City Hospital, Cambridge, Mass., and Dr. Robert F. Bradley, Jr., Visiting Physician, Northeast Deaconess Hospital, Boston, Mass.

Dr. John H. Bland, F.A.C.P., Associate Professor of Medicine, University of Vermont College of Medicine, Burlington, Vt., will spend a year at the Rheumatism Research Center of the University of Manchester, England. He will also visit several European universities and make a comparative study of medical education methods in England, Europe, and the United States during his leave of absence.

Dr. Clayton G. Loosli, F.A.C.P., Dean of the University of Southern California School of Medicine, Los Angeles, Calif., has announced the appointment of Dr. Thomas H. Brem, F.A.C.P., as Chairman of the Department of Medicine in the School of Medicine. Dr. Brem succeeds Dr. Paul Starr, F.A.C.P., who retires after serving in this capacity from 1948–55. During the past three years Dr. Starr had shared the Chairmanship with Dr. Brem and was responsible for research in the Department.

Dr. Lowell A. Rantz, F.A.C.P., Stanford, Calif., Dr. Dwight L. Wilbur, F.A.C.P., San Francisco, Calif., and Dr. Albert M. Snell, F.A.C.P., Palo Alto, Calif., are serving as members of a Committee to select a replacement for Dr. David A. Rytand,

F.A.C.P., who has requested he be relieved of his executive duties while continuing as Professor of Medicine at the Stanford University School of Medicine. Dr. Rantz was also recently named Associate Dean of the Stanford University School of Medicine on September 1, 1958. In this capacity he succeeds Dr. Jay Ward Smith, (Associate), who resigned to resume private practice.

Dr. C. H. Hardin Branch, F.A.C.P., Salt Lake City, Utah, discussed the subject, "Psychotherapy in the General Practitioner's Office," and Dr. William H. Gordon, Sr., F.A.C.P., Lubbock, Tex., discussed "Is It Angina?" at the 10th Scientific Assembly of the California Academy of General Practice in San Francisco, Calif., October 5–18, 1958.

Four Fellows of the College participated in the International Symposium on Tuberculosis held in Philadelphia, Pa., November 20-22, 1958, and sponsored by the Deborah Sanatorium and Hospital. The Fellows and their titles were: Dr. Walsh McDermott, New York, N. Y., "Chemotherapeutic Prophylactic Measures for Tuberculosis"; Dr. William B. Tucker, Washington, D. C., "The Hospital and Home, Respective Roles in Tuberculosis Management," and "Chemotherapy of Tuberculosis"; Dr. Katharine R. Boucot, Philadelphia, Pa., "Tuberculosis Case-Finding: The Problem in the General Population, Schools and Hospital," and Dr. David A. Cooper, Philadelphia, Pa., "The Future Problem of Tuberculosis: Program for its Control."

Captain Eugene V. Jobe, F.A.C.P., (MC), U. S. Navy, was a representative of the Surgeon General of the Navy at the 69th Annual Meeting and Preconference Meeting of the Association of American Medical Colleges held in Philadelphia, Pa., October 11–15, 1958.

Dr. Julius Bauer, F.A.C.P., Los Angeles, Calif., delivered a lecture on "Sickle Cell Disease as a Circulatory Problem," before the Society of Internal Medicine in Vienna, Austria, on October 23 and one on "Constitutional Predisposition to Diseases in the Past and at Present," before the Society of Physicians in Vienna on October 24.

Dr. B. Shannon Gallaher, (Associate), has been named Assistant Professor of Medicine at the Medical College of Georgia, Augusta, Ga.

Dr. W. B. Frommeyer, Jr., F.A.C.P., Chairman of the Department of Medicine at the Medical College of Alabama, Birmingham, Ala., was elected President-Elect, and Dr. Maxwell Moody, Jr., (Associate), of Tuscaloosa, Ala., was installed as President of the Alabama Heart Association at its recent annual meeting.

Dr. Charles E. Porter, F.A.C.P., Fairfield, Ala., was named President, and Dr. Wood S. Herren, (Associate), Birmingham, Ala., was elected Vice President, at a recent meeting of the Birmingham Society of Internists.

Dr. John A. Reed, F.A.C.P., Washington, D. C., received the Banting Medal from the American Diabetes Association at a recent meeting.

Dr. John C. Rose, (Associate), Associate Professor of Medicine at the Georgetown University School of Medicine, Washington, D. C., has been recently appointed Acting Chairman of the Department of Physiology at that institution.

Recently elected members to the Board of Directors of the Washington (D. C.) Heart Association were: Drs. Henry D. Ecker, F.A.C.P.; John F. Finnegan, (Associate); and Edward D. Freis, F.A.C.P., Washington, D. C.

Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., has been appointed a member of the Scientific Advisory Board of Consultants of the Armed Forces Institute of Pathology.

Rear Admiral Bartholomew W. Hogan, F.A.C.P., (MC) U. S. Navy, Surgeon General and Chief of the Bureau of Medicine and Surgery, Navy Department, Washington, D. C., was awarded the "Peruvian Cross of Merit" by the President of the Republic of Peru and the Peruvian Navy. Rear Admiral Luis Edgardo Llosa, Naval Attache, Embassy of Peru, Washington, D. C., presented the decoration to Admiral Hogan in celebration of the Peruvian Navy Day, October 8, 1958.

Captain Charles L. Ferguson, (Associate), (MC), U. S. Navy, Commanding Officer of the Naval Hospital, Philadelphia, Pa., presided over the 9th Annual Military Medico-Dental Symposium on Space Medicine for all of the Army Forces at the U. S. Naval Hospital, Philadelphia, Pa., October 24–27, 1958.

Dr. Andrew C. Woofter, F.A.C.P., Parkersburg, W. Va., was elected Vice President at a recent meeting of the West Virginia Heart Association at Fairmont, W. Va.

Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C., received the "Medallion and Citation" of the American Cancer Society at the South Carolina Division's Annual Meeting. The award was for "outstanding service in the cause of cancer control."

Dr. Elston L. Belknap, Sr., F.A.C.P., Milwaukee, Wis., presented a paper on the subject, "Health Control in Storage Battery Manufacture," at the Lead Hygiene Conference sponsored by the Lead Industries Association and held at Chicago, Ill., November 6-7, 1958. Dr. Lemuel C. McGee, F.A.C.P., Wilmington, Del., was Chairman of one of the three conference sessions.

Drs. John H. Mitchell, F.A.C.P., Columbus, Ohio, and William B. Sherman, F.A.C.P., New York, N. Y., were members of a panel which discussed "The Single Repository Injection Treatment of Hay Fever" at the meeting of the New York Allergy Society held November 17, 1958.

Dr. Joseph E. Flynn, F.A.C.P., Columbia, Mo., Chairman of the Research Committee of the American Society of Clinical Pathologists, has announced the awarding of 13 prizes of \$100 each to medical students for meritorious research. Funds for the grants are provided from royalties derived from the photelometer designed by Drs. Arthur H. Sanford, F.A.C.P., Rochester, Minn., and Charles Sheard, F.A.C.P., Stamford, Conn.

Three Fellows of the College were speakers at the 10th Annual Symposium on Heart Disease jointly sponsored by the Washington State Heart Association and the Washington State Department of Health in Seattle, Wash., October 17–18, 1958. The Fellows and their subjects were: Dr. Carleton B. Chapman, F.A.C.P., Dallas, Tex., "Hemodynamic Effects of Exercise" and "Hypertensive Patients to Physical Exercise"; Dr. Lewis Dexter, F.A.C.P., Boston, Mass., "Clinical-Physiological Correlations of Congestive Heart Failure" and "Cardiac Output and Congestive Heart Failure," and Dr. James V. Warren, F.A.C.P., Galveston, Tex., "Treatment of Congestive Failure" and "Natural History of Hypertensive Disease in Man and Hypertension in Giraffes."

Dr. Leonidas H. Berry, F.A.C.P., Clinical Assistant Professor of Medicine, University of Illinois College of Medicine, Chicago, Ill., recently was awarded a gold medal by the National Medical Association "for the most distinguished service rendered to the profession on the National level." He was honored for "his pioneering efforts and success in the Specialty of Diseases of the Stomach, and the 'Berry Plan' for treatment of Drug Addicts."

Colonel Charles R. Mueller, F.A.C.P., (MC) U. S. Army (Retired), Washington, D. C., President of the Association of Military Surgeons of the United States, discussed the subject, "Dynamic Medicine and Rehabilitation in the Space Age," at the 65th Annual Convention of the Association held in Washington, D. C., November 16, 1958. Brigadier General Don D. Flickinger, F.A.C.P., U. S. Air Force (MC), served on a panel on the "Problems of Space" at the same meeting.

Three members of the College participated in the program of the 6th Annual Symposium on Diabetes Mellitus sponsored by the New Jersey Diabetes Association and the New Jersey State Department of Health and held at Newark, N. J., October 29, 1958. Dr. Harold J. Jeghers, F.A.C.P., Jersey City, moderated a discussion. Dr. George E. Schreiner, (Associate), Washington, D. C., discussed the subject, "Renal Biopsy Pathology in Diabetic Patients," and Dr. Walter Redisch, F.A.C.P., New York, N. Y., discussed "Relation Between Diabetes and Obliterative Arteriosclerosis."

Dr. Stephen C. F. Mahady, (Associate), the former Director of the Broadacres Sanatorium, Utica, N. Y., was recently named Director of the State Out-Patient Chest Clinic at the Sanatorium.

Dr. Glenn W. Irwin, Jr., F.A.C.P., Indianapolis, Ind., discussed the subject, "Current Status of the Correct Management of Thyroid Disorders," at the 109th Annual Meeting of the Indiana State Medical Association held in Indianapolis, Ind., October 12-15, 1958.

Dr. William H. Sebrell, Jr., F.A.C.P., Director, Institute of Nutrition Sciences, Columbia University College of Physicians and Surgeons, New York, N. Y., was a speaker at a symposium on "Advances in Human Nutrition" sponsored by the H. J. Heinz Company as a part of the dedicating ceremonies for the new Heinz Research Center held in Pittsburgh, Pa., October 13-14, 1958.

Dr. Donald L. Kegaries, F.A.C.P., Rapid City, S. D., was elected President of the South Dakota State Board of Medical and Osteopathic Examiners at a meeting of the Board in Rapid City, S. Dak., in August, 1958.

Three Fellows of the College were elected officers at a recent meeting of the Chicago Society of Internal Medicine. They are: Drs. Ernest G. McEwen, Evanston, Ill., President; Wright R. Adams, Chicago, Ill., Vice President, and Franklin A. Kyser, Evanston, Ill., Secretary-Treasurer.

Dr. Theodore R. Van Dellen, F.A.C.P., Assistant Dean of the Northwestern University Medical School and Associate Editor of the ILLINOIS MEDICAL JOURNAL was awarded the 1958 distinguished service citation of the American Writers' Association at the Annual Meeting of the Association in Chicago in September, 1958.

Two Fellows of the College were active in the 13th Annual Meeting of the Southeastern Allergy Association held in Atlanta, Ga., October 31-November 1, 1958. Dr. Merle W. Moore, Portland, Ore., President of the American College of Allergists, discussed the subject, "Clinical Evaluation of Stock Vaccine in the Treatment of Bronchial Asthma," and Dr. Oscar Swineford, Jr., Charlottesville, Va., discussed "Basic Information on Desensitization."

Dr. Wilfred Dorfman, F.A.C.P., Brooklyn, N. Y., was named President-Elect, and Dr. M. Murray Peshkin, F.A.C.P., New York, N. Y., Historian, at the recent Annual Meeting of the Academy of Psychosomatic Medicine held in New York, N. Y.

Dr. Herman A. Dickel, F.A.C.P., Portland, Ore., was elected President of the Oregon State Medical Society at the Annual Meeting held in Portland, Ore., September 3-5, 1958.

Dr. Ralph H. Nestmann, (Associate), Charleston, W. Va., has been elected President of the West Virginia Tuberculosis and Health Association.

Rear Admiral Irwin L. V. Norman, F.A.C.P., (MC) U. S. Navy, Inspector General, Medical, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., inspected the medical facilities at the U. S. Naval Hospital, St. Albans, N. Y., October 6-10, 1958. Captain R. D. Ross, F.A.C.P., (MC) U. S. Navy, Professional Division, aided in the inspection.

Dr. George H. Garrison, F.A.C.P., Oklahoma City, Okla., was one of three physicians appointed by the Chairman of the American Medical Association Board of Trustees to serve as Health Project Advisors to the United States Junior Chamber of Commerce.

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., retired as the American Medical Association Delegate from West Virginia at the Clinical Meeting of the Association in December. He had served in this capacity since 1934.

Dr. Elmer L. Severinghaus, F.A.C.P., Professor of Public Health Nutrition in the School of Public Health and Administrative Medicine at Columbia University College of Physicians and Surgeons, New York, N. Y., gave a series of five lectures in the field of human nutrition before the Medical Association of Puerto Rico in San Juan, October 6-10, 1958. He also lectured before the senior students in Home Economics at the University in Puerto Rico.

Dr. John C. Beck, (Associate), Montreal, Quebec, Can., presented a paper entitled "Endocrine Disturbances Caused by Pituitary and Hypothalamic Tumors" at the 5th Annual Meeting of the Canadian Society for the Study of Fertility held in London, Ontario, Can., October 31-November 1, 1958.

Dr. Carroll M. Leevy, F.A.C.P., Jersey City, N. J., moderated a symposium on infectious diseases and Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., discussed the subject, "What's ahead for American Medicine," at the 11th Annual Meeting of the Jersey City Medical Center Alumni Association held in that city November 5, 1958.

Dr. Carl C. Fischer, F.A.C.P., Chairman of the Department of Pediatrics, Hahnemann Medical College and Hospital of Philadelphia, was named Health Service Director at Girard College, Philadelphia, Pa., starting September 2, 1958. He will continue his duties at Hahnemann College.

Dr. O. Spurgeon English, F.A.C.P., Head of the Department of Psychiatry, Temple University School of Medicine, Philadelphia, Pa., was a speaker at the Conference on Schizophrenia and the Family held at the College on October 9-10, 1958.

Dr. Horatio B. Sweetser, Jr., F.A.C.P., Minneapolis, Minn., discussed the field of Osteopaths at a discussion on "Cultism and Limited Licensees" at the Annual Meeting of the North Central Medical Conference held at Minneapolis, Minn., October 11-12, 1958.

Dr. John R. Hogness, (Associate), Seattle, Wash., was recently appointed Medical Director of the University Hospital. He will begin on a half-time basis and will assume full-time responsibilities when the hospital opens in May, 1959. He will continue his research and teaching duties in the Department of Medicine of the University of Washington School of Medicine.

Dr. Nathan Beckenstein, F.A.C.P., Brooklyn, N. Y., Director of the Brooklyn State Hospital, discussed the subject, "Various Types of EST and Their Indications," at the 3rd Annual Meeting of the Eastern Psychiatric Research Association held in Brooklyn, N. Y., October 23-25, 1958.

Dr. Irvine H. Page, F.A.C.P., Cleveland, Ohio, gave the Annual Lecture at the Meeting of the American College of Preventive Medicine held in St. Louis, Mo., October 29-30, 1958. His subject was "Arteriosclerosis—Its Multifaceted Nature."

Dr. Seymour K. Fineberg, F.A.C.P., Chief of the Metabolic Service at Harlem Hospital, New York, N. Y., was recently appointed Director of Medical Education at that institution.

Dr. Lewis B. Flinn, F.A.C.P., Wilmington, Del., Governor for Delaware of the American Diabetes Association, was active in the recent organization of the Delaware Diabetes Association. Charter membership includes the following College members from Wilmington, Del.: Drs. Ward W. Briggs, F.A.C.P.; Herbert M. Baganz, Jr. (Associate); Marvin H. Dorph, (Associate), and William T. Hall, Sr., (Associate).

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla., spoke on "Disorders of the Thyroid Gland" at the 10th Annual Postgraduate Assembly of the Endocrine Society early in October at the State University of New York Upstate Medical Center, Syracuse, N. Y. Dr. Turner is Secretary-Treasurer of the Endocrine Society.

Dr. Edward E. Fischel, F.A.C.P., New York, N. Y., was recently appointed Associate Clinical Professor of Medicine at the Albert Einstein College of Medicine of Yeshiva University. He will continue his full-time position as Director of the Department of Medicine at the Bronx Hospital, New York, N. Y.

Dr. Harold R. Merwarth, F.A.C.P., Clinical Professor of Neurology, State University of New York Downstate Medical Center at New York City, gave his inaugural address as President of the New York Neurological Society at the combined meeting of the New York Neurological Society and the Section of Neurology and Psychiatry of the New York Academy of Medicine at New York, N. Y., on October 9, 1958. The subject of his presentation was "Re-evaluation of Hemiplegia of Venous Origin."

Dr. William H. Harris, Jr., F.A.C.P., Richmond, Va., Secretary-Treasurer of the Virginia Section of the American College of Physicians, reports that 75 members and six guests attended a luncheon meeting during the Annual Meeting of the Medical Society of Virginia in Richmond, October 13, 1958. Dr. Charles M. Caravati, F.A.C.P., Richmond, Va., A.C.P. Governor for Virginia, was the principal speaker. The date of the Virginia Regional Meeting which will be Saturday, March 21, 1959, Hot Springs, Va., was announced. Dr. T. Dewey Davis, F.A.C.P., Richmond, Va.,

retiring Chairman of the Section, presided. Dr. R. Earle Glendy, F.A.C.P., Roanoke, Va., was elected Chairman and Dr. William H. Harris, Jr., F.A.C.P., Richmond, Va., was re-elected Secretary-Treasurer (both offices for the year 1959).

Dr. Charles S. Morrow, F.A.C.P., Wilkes-Barre, Pa., discussed the subject, "The Pneumonoconioses," before the Mississippi Valley Medical Society in Chicago, Ill., September 26, 1958. He participated as a panel member, discussing the subject, "Public Education in the Control of Heart Disease," at the Pennsylvania Heart Association Meeting in Philadelphia, Pa., September 20, 1958.

Dr. Harold N. Neu, F.A.C.P., Professor and Head of the Department of Medicine, Creighton University School of Medicine, Omaha, Nebr., will direct a program "to implement personnel needed to help train medical students and residents in the modern concepts of rehabilitation." The project will be financed by five annual grants from the Office of Vocational Rehabilitation, Washington, D. C.

Dr. Richard H. Freyberg, F.A.C.P., New York, N. Y., discussed the subject, "Newer Concepts in Diagnosis and Treatment of Rheumatoid Arthritis," at the 3rd Samuel E. Cohen Memorial Teaching Day held at Binghamton, N. Y., October 1, 1958,

Dr. David Grob, (Associate), Associate Professor of Medicine at The Johns Hopkins University School of Medicine, Baltimore, Md., has been appointed Director of Medical Services at Maimonides Hospital, Brooklyn, N. Y., and Professor of Medicine at the State University of New York Downstate College of Medicine at New York City.

Dr. Harold G. Wolff, F.A.C.P., New York, N. Y., and Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, Pa., were speakers at a symposium on "The Brain and Diabetes Mellitus" sponsored by the Clinical Society of the New York Diabetes Association and held in New York, N. Y., October 10, 1958. The subjects of their papers were "Role of the Highest Integrative Functions of the Central Nervous System in Disease" and "Clinical Experience with Oral Hypoglycemic Agents," respectively.

Four Fellows of the College from the State of Pennsylvania were moderators of panels at the 108th Annual Session of the Medical Society of the State of Pennsylvania at Philadelphia, Pa., October 12–17, 1958. The Fellows and the title of the panels they moderated were: Dr. Wendell B. Gordon, Pittsburgh, "Trends in Medical Care"; Dr. Thaddeus S. Danowski, Pittsburgh, "Steroids—Uses and Abuses"; Dr. Constantine P. Faller, Harrisburg, "Reduction of Mortality and Morbidity in Automobile Accidents—The Physicians' Responsibility," and Dr. Allen W. Cowley, Harrisburg, "The Chronically Tired Patient—An Important Complaint."

Dr. Louis G. Jekel, Sr., (Associate), Phoenix, Ariz., presided as President at the Annual Meeting of the Southwestern Medical Association held in Tucson, Ariz., October 23-25, 1958. Dr. George C. Andrews, Jr., F.A.C.P., New York,

N. Y., presented a paper entitled "Diagnosis and Treatment of Common Dermatoses of the Hands"; Dr. Henry J. Koch, Jr., (Associate), Tucson, Ariz., "Thyroid Physiology and Brain Function—Alcoholism and Hangovers," and Dr. Reginald H. Smart, (Associate), Los Angeles, Calif., "Recognition and Treatment of Respiratory Acidosis."

Dr. Leroy E. Burney, F.A.C.P., Surgeon General, Public Health Service, Washington, D. C., was a speaker at the dedication of the new National Orthopaedic and Rehabilitation Hospital, Arlington, Va., October 25, 1958.

Dr. Edwin P. Jordan, F.A.C.P., Executive Director, American Association of Medical Clinics, Charlottesville, Va., reports that the following physicians were elected officers at a recent meeting of the Association held in San Francisco, Calif.: Dr. J. W. St. Geme, Los Angeles, Calif., President; Dr. Russel V. Lee, Palo Alto, Calif., President-Elect, and Dr. Joseph B. Davis, Marion, Ind., Secretary-Treasurer.

Dr. Helen B. Taussig, F.A.C.P., and Dr. Alfred Blalock, both of The Johns Hopkins University School of Medicine, Baltimore, Md., were joint recipients of the \$25,000 which accompanied the Gairdner Foundation Award of Merit. Dr. Charles A. Ragan, Jr., F.A.C.P., New York, N. Y., also received a \$5,000 Gairdner Foundation Annual Award. These were the first international awards in arthritis and heart disease to be made by the Gairdner Foundation of Toronto, Ontario, Can. Dr. Taussig and Dr. Blalock were recognized for their initial development of what is known to the public as the "blue-baby operation." Dr. Ragan, together with Dr. Harry M. Rose, was recognized for the discovery of the first practical laboratory test in the diagnosis of rheumatoid arthritis.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., presented a paper entitled "Clinical Experience with Chlorpropamide" at the World Conference on Chlorpropamide" held by the New York Academy of Sciences in New York, N. Y., September 25-27, 1958.

Dr. George L. Waldbott, F.A.C.P., Detroit, Mich., presented a paper entitled "Fluorosis from Drinking Water" at a meeting of the Swedish Medical Society in Stockholm, Sweden, November 4, 1958. He also presented a paper on "Unusual Complications of Bronchial Asthma" at a meeting of the International Congress of Allergy in Paris, France, October 19–26, 1958.

Dr. Thomas F. Frawley, F.A.C.P., of Albany Medical College of Union University, was a guest speaker at the 6th Annual Scientific Session of the Florida Diabetes Association at Miami Beach, Fla., October 30-31, 1958.

Brigadier General Elbert DeCoursey, F.A.C.P., (MC), U. S. Army, Commandant of the Army Medical Service School at Brooke Army Medical Center, Fort Sam Houston, Tex., recently was promoted to Major General. Brigadier General Clem-

ent F. St. John, F.A.C.P., (MC), U. S. Army, Commander of Brooke Army Hospital and members of the staff at 4th Army Headquarters attended the ceremonies marking his advancement. General DeCoursey has won international acclaim for his studies in radiation pathology. He was Director of the Army Group at Nagasaki which investigated the effects of the 1945 atomic explosion.

Dr. Lee D. Cady, F.A.C.P., Manager, Veterans Administration Hospital, Houston, Tex., was elected to the Executive Committee of the new Medical School—Teaching Hospital Section, of the Association of American Medical Colleges at the meeting of the Association in Philadelphia, Pa., October 13–15, 1958.

Dr. B. J. Kennedy, (Associate), Associate Professor of Medicine, University of Minnesota Medical School, was a guest lecturer at the 11th Annual Scientific Meeting of the Detroit Institute of Cancer Research on October 29. He spoke on "The Physiological Responses During Hormone Therapy of Breast Cancer."

Dr. Paul H. Morton, F.A.C.P., presided at the 8th Annual Symposium of the San Diego Heart Association, held at the U. S. Naval Hospital, San Diego, Calif., on October 31, 1958. Those appearing on the program included Dr. Hans H. Hecht, F.A.C.P., Salt Lake City, Utah; Dr. Helen B. Taussig, F.A.C.P., Baltimore, Md.; Sir George Pickering, F.R.C.P., F.A.C.P. (Hon.), Oxford, England, and Dr. Dwight E. Harken, F.A.C.S., Boston, Mass. The subject was "Hypertension." Sir George Pickering was also the speaker at the evening banquet. His subject was "The Proper Use of Words."

OBITUARIES

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

- Dr. John Andrew Beyer, (Associate), Madison, Wis., November 3, 1958
- Dr. Willard David Mayer, F.A.C.P., Detroit, Mich., August 8, 1958
- Dr. Orman Clarence Perkins, F.A.C.P., Brooklyn, N. Y., August 18, 1958
- Dr. Irving J. Sands, F.A.C.P., Brooklyn, N. Y., October, 1958
- Dr. Harry Dickey Sewell, F.A.C.P., Wellesley Hills, Mass., August 25, 1958
- Dr. Emanuel Yadkowsky, (Associate), Newark, N. J., August 23, 1958

BRIG. GEN. HENRY CLAY COBURN, JR., (MC), U. S. ARMY, (Ret.)

Brig. Gen. Henry Clay Coburn, Jr., F.A.C.P., MC, U. S. Army, retired, died of a heart attack October 22, 1958, at his home in Haddonfield, New Jersey. He was born in Washington, D. C., on August 5, 1879.

General Coburn received an M.D. Degree from Columbia University (now George Washington University) in Washington, D. C., in 1903. After an internship at George Washington Hospital, he was in private practice here until he entered the Army Medical Corps as a First Lieutenant in 1908.

General Coburn graduated with honors from the Army Medical School in 1909. He received postgraduate training in internal medicine at The Johns Hopkins University School of Medicine, in 1920.

He served in the Philippines and North China from 1910 to 1913. In the First World War he organized Base Hospital 17 at Detroit and took it to Dijon, France. Later he became Surgeon of Base Section 2, Bordeaux, and for his services to France was made a Chevalier in the Legion of Honor.

From 1921 to 1924, General Coburn was Chief of Medical Service at Walter Reed General Hospital, Washington, D. C. After that he held similar posts at Fitzsimons General Hospital, Denver, Colorado, and the U. S. Army Hospital at Fort Sam Houston, Texas. In 1936 he was again made Chief of Medical Service at Walter Reed General Hospital where he served until 1939, when he became Surgeon at Fort Bragg, N. C. He held this post until his retirement in 1946. General Coburn was awarded the Legion of Merit for his services at Fort Bragg.

General Coburn was a member of the American Medical Association, a Fellow of the American College of Surgeons and of the American College of Physicians.

He is survived by his wife, Elma S. of 274 Kings Highway East, Haddonfield, New Jersey; two daughters, Mrs. Neil D. Cole, of Pittsburgh, Pennsylvania, and Mrs. Carl K. Warren, of Hawaii, and two grandchildren.

Major General Silas B. Hays, (MC), U. S. Army, F.A.C.P. Governor for U. S. Army

DR. BEN HUNTER COOLEY

Dr. Ben Hunter Cooley, F.A.C.P., of El Paso, Texas, died of carcinoma of the lung on September 20, 1958, in El Paso, Texas. He was born at Smithville, Texas, on November 26, 1894.

He received preliminary education at the Fort Worth, Texas, public schools, and an M.D. degree from the University of Oklahoma School of Medicine, Norman, Oklahoma, in 1921. He interned at the Oklahoma University Hospital, and engaged in private practice in Norman, Oklahoma, in 1922 where he remained until 1941.

He was Clinical Instructor in Medicine, University of Oklahoma School of Medicine from 1923 to 1927, and member of the staffs of the University of Oklahoma Infirmary and the American Legion Hospital. Dr. Cooley served in the Army Medical Corps during World Wars I and II, and was Chief of Medical Section, School of Medical Department Technicians, William Beaumont General Hospital, El Paso, Texas, from 1941 until his retirement in 1946 with the rank of Lieutenant Colonel (MC) U. S. Army Reserve. Following his military reserve retirement he entered private practice in El Paso, and was Chief of Medical Service, Providence Memorial Hospital for 1953–1955, Vice Chief of Staff, El Paso General Hospital since 1955 and Chief of Staff, Southwestern General Hospital since 1955.

Dr. Cooley was a member of the American Medical Association; the Oklahoma State Medical Association; the Cleveland County (Oklahoma) Medical Society (President 1932); the Southern Medical Association; the Texas Medical Association; the El Paso Medical Society; the Texas Heart Association; the Texas Academy of Internal Medicine; and a Fellow of the American College of Physicians.

Dr. Cooley is survived by his widow, Mrs. Eve P. Cooley, 2020 Caples Circle, El Paso, Texas.

VICTOR E. SCHULZE, M.D., F.A.C.P., Governor for Texas

DR. EUGENE HENRY DRAKE

Dr. Eugene Henry Drake, F.A.C.P., born on August 7, 1892, in Pittsfield, Maine, died from tetanus in Portland, Maine, on October 4, 1958. He apparently contracted this infection while working on his farm which had been his hobby since returning from World War II.

Dr. Drake graduated from Bates College in 1914 and from Bowdoin Medical School in 1919, following which he interned for one year at the Maine General Hospital. After a few years of General Medicine, he studied Cardiology with Dr. Paul Dudley White at the Massachusetts General Hospital and then spent a year in Internal Medicine in London and Vienna.

From 1937 until 1947, except for time spent in Naval Service in World War II, he was Chief of the Medical Service of the Maine General Hospital. From 1947 until 1956, he was Chief of the Section on Cardiology and since 1956 was Chief Emeritus of the Department of Medicine at the Maine Medical Center (formerly the Maine General Hospital). He organized the first heart clinic in Maine in 1925 and was instrumental in the final development of a recognized Cardiac Research and teaching department at the Maine Medical Center. The Maine Heart Association of which he was Past President was organized under his guidance.

Dr. Drake was a member of the following: American Medical Association; Maine Medical Association (President 1952-53); Portland Medical Club (President 1928); Cumberland County Medical Society; American Heart Association (Member, Board of Directors); New England Heart Association (Ex-Vice President); Maine Heart Association (President 1951); Diplomate, American Board of

Internal Medicine; Fellow, American College of Physicians, 1929 and Life Member 1941. He was a Governor of the American College of Physicians (1938-48).

Dr. Drake had a large consulting and private practice, and among his patients were physicians and their families. He was a scholar, an excellent teacher and a stimulant to younger physicians in the State where he was active until his last illness.

He is survived by his wife, Effie H. Drake, and two sisters.

E. R. BLAISDELL, M.D., F.A.C.P., Governor of Maine

DR. J. W. EARL ELLENBERGER

J. W. Earl Ellenberger, M.D. (Associate) of Pittsburgh, Pennsylvania, died March 16, 1958.

Dr. Ellenberger was born in 1887. He received his medical education at the Jefferson Medical College of Philadelphia, graduating in 1911. He interned at the Allegheny General Hospital, Pittsburgh, Pennsylvania, and received postgraduate education at the Mount Alto Tuberculosis Sanatorium and the Cresson State Sanatorium for Tuberculosis.

Dr. Ellenberger was a member of the Senior Staff at the Pittsburgh Hospital since 1925. During World War I, Dr. Ellenberger served as a Captain in the A.E.F.

He was a member of the American Medical Association; the Medical Society of the State of Pennsylvania; the Allegheny County Medical Society, and the Wilkinsburg Medical Society. Dr. Ellenberger became an Associate of the College in 1924.

Dr. Ellenberger is survived by his widow, Mrs. Ethel M. Ellenberger of Wilkinsburg.

Frank John Gregg, M.D., F.A.C.P., Governor for Western Pennsylvania

DR. WILLIAM VAN VALZAH HAYES

Dr. William Van Valzah Hayes, F.A.C.P., was born on September 22, 1867, at Lewisburg, Pennsylvania, and died on June 27, 1958, in Greenwich, Connecticut, of multiple cerebral vascular accidents.

Dr. Hayes received his A.M. degree at Bucknell University; and his M.D. degree at Columbia University College of Physicians and Surgeons in 1893. He interned at the Sloane Maternity and the New York Foundling Hospitals, 1894-96.

His academic and hospital appointments were as follows: Professor of Diseases of The Digestive System, New York Polyclinic Medical School and Hospital, 1904–17; Consulting Physician in Gastroenterology, New York Polyclinic Medical School and Hospital and St. John's Riverside Hospital, Yonkers, New York, 1917–47. He retired in 1947.

Dr. Hayes was a member of the following: American Medical Association; Medical Association of Greater New York; Medical Society of the State of New York; New York County Medical Society; New York Gastroenterology Association (President, 1924); New York Medical Union (President 1930-32); and the New

York Academy of Medicine. He was a diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1926.

It is with regret that his loss is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor, Eastern Division
New York State

DR. JOHN PHILLIPS HENRY

Dr. John Phillips Henry, F.A.C.P., of Memphis, Tennessee, died on July 4, 1958, of a massive gastric hemorrhage. He was born at Bolton, Mississippi, in 1893. He received his medical education at the University of Tennessee College of Medicine, receiving the M.D. degree in 1917. Then he served an internship at Bellevue Hospital in New York City and later was House Physician at Charity Hospital in Louisville, Kentucky. During World War I he was a Lieutenant in the Medical Corps of the Army.

He became interested in the field of Allergy immediately after World War I and practiced this specialty until shortly before his death, in the Henry Hay Fever and Asthma Clinic, which he established. Dr. Henry carried a clinical appointment on the faculty of the University of Tennessee College of Medicine as an Associate Professor since 1923, with his teaching interests in the field of Allergy, and contributed to the literature in the area of his special interest. He was a member of the staff of the Baptist Memorial and John Gaston Hospitals.

Dr. Henry was a member of his local and State medical organizations, the American Medical Association, the American College of Allergy, of which he was the Second Vice-president in 1949, the Association for the Study of Allergy, the Southern Medical Association, and has been a Fellow of the American College of Physicians since 1931.

Dr. Henry was active in the affairs of the Episcopal Church. Though he was a golfer, his main hobby was photography, and he was always an avid reader. He had the respect of all of his colleagues, and in his death his patients lost a faithful physician. He is survived by his wife, Mrs. Elizabeth Henry; his mother, Mrs. W. T. Henry of Rayville, La.; two sons, John Phillips Henry, Jr. and Emil William Henry of Memphis; a sister, Mrs. Allen Cook of Rayville, and three grandchildren.

RUDOLPH H. KAMPMEIER, M.D., F.A.C.P., Governor for Tennessee

DR. ALLAN S. KENNEDY

Dr. Allan S. Kennedy, a Fellow of the American College of Physicians since 1938, died suddenly at his home, 41 Mill Street, South Waterdown, Ontario, on September 13, 1958, at the age of 59.

Born in Jamaica, British West Indies, Dr. Kennedy moved to Canada with his parents in early childhood. He graduated from the University of Toronto Faculty of Medicine, in 1927 and thereafter underwent post graduate training which included an internship in the Toronto General Hospital, a Banting Fellowship in the Department of Pharmacology, University of Toronto, and a considerable amount of cardiologic and electrocardiographic training in Toronto and Boston.

Dr. Kennedy was a member of the Toronto Academy of Medicine since 1931. He became a member of the Hamilton Academy of Medicine in 1933 and was President of this organization in 1951. From that date until his untimely death, he served as Chairman of the Committee on Education of the Hamilton Academy and in this capacity he developed plans for annual Tutorial Courses for members of the Academy designed to keep these practising physicians abreast of the rapidly changing field of their profession. Dr. Kennedy always felt strongly the importance of this work and spent a great deal of time and effort in making these tutorial sessions a rich opportunity for stimulating and creative discussion. In 1954 Dr. Kennedy organized the first public medical forum sponsored by the Hamilton Academy. All this work in medical and lay education was very dear to his heart and from it he derived very deep satisfaction. He himself made a number of contributions to medical literature in the form of articles on various aspects of internal medicine.

From 1930 to 1942, Dr. Kennedy was Physician in Charge of the Department of Internal Medicine, Mountain Sanatorium, at Hamilton. He was a member of the Attending Medical Staff of the Hamilton General Hospital from 1946 until his death. In January 1950 he became a Consultant in Medicine for the Department of Veterans Affairs.

Dr. Kennedy was a member of the Ontario Medical Association and the Canadian Medical Association. In 1946 he was certified as a Specialist in Internal Medicine by the Royal College of Physicians and Surgeons of Canada. He was a charter member of the Canadian Heart Association.

Dr. Kennedy was an able and much loved clinician who gave generously of his time and energy to the care of his patients. He left a host of friends and colleagues who will long cherish his memory.

W. FORD CONNELL, M.D., F.A.C.P.,
Governor for Ontario

DR. JOHN ALEXANDER MACDONALD

Dr. John A. MacDonald, F.A.C.P., died June 17, 1958, at the age of 81, in his home at Glenwood Lodge, Interlaken, New York, where he had lived since his retirement from active practice in 1951. Born in Wooster, Ohio, on May 8, 1877, Dr. MacDonald attended Miami University, Oxford, Ohio, and graduated from Rush Medical College in 1901. After his internship at Presbyterian Hospital, Chicago, he attended The Johns Hopkins University School of Medicine and the New York Post-Graduate Medical School.

During World War I Dr. MacDonald served as a Captain in the Medical Corps of the U. S. Army, and was Chief of the Medical Service of General Hospital No. 35. After the war he limited his practice to diagnostic and consultative service in internal medicine. Dr. MacDonald practiced medicine in Indianapolis from 1907 until his retirement.

He began his service in the City Dispensary in 1908 and was a Member of the Staff of the Indianapolis General Hospital until 1938. As Clinical Professor of Medicine at the Indiana University School of Medicine from 1932 until his retirement, he took an active part in teaching. Dr. MacDonald served as a Consultant at the University Hospitals.

He was elected to Fellowship in the American College of Physicians in 1927, and was a Charter Member and Founder of the Central Society for Clinical Research. In 1937 he was named a Diplomate of the American Board of Internal Medicine. He was also a member of the American Medical Association; the Inter-State Post-

Graduate Assembly; the Indiana State Medical Association; the Indianapolis Academy

of Medicine, and the Indianapolis Medical Society.

Dr. MacDonald maintained a keen interest in young men, and by example and guidance was able to direct many students and house officers toward a career in internal medicine. He represented all of the qualifications of a true physician. His interest in clinical research and new therapeutic agents and diagnostic methods was maintained through many years of strenuous private practice. Throughout his life Dr. MacDonald was respected by his colleagues and by his patients.

Dr. MacDonald is survived by his wife. To her, his colleagues in The College

extend their sincere sympathy.

KENNETH G. KOHLSTAEDT, M.D., F.A.C.P., Governor for Indiana

DR. RALPH JAMES MCMAHON

Dr. Ralph James McMahon, F.A.C.P., died suddenly on September 10, 1958, of coronary thrombosis in Binghamton, New York, while playing golf. He was born in Batavia, New York, August 29, 1898, the community in which he received his undergraduate education. The degree of Doctor of Medicine was awarded him in 1921 at the University of Buffalo School of Medicine. The following year he married Laura Elizabeth Cook of Orchard Park.

His postgraduate training included: University of Pennsylvania School of Medicine, 1927-28; Trudeau School of Tuberculosis, 1929; Harvard Medical School, 1931-32; University of Minnesota Medical School, 1943 and University of Pennsyl-

vania School of Medicine, 1945-49.

He was Attending Physician at the Binghamton City and the Charles S. Wilson Memorial Hospitals as well as Attending Physician and Chairman of the Medical Section of Our Lady of Lourdes in Binghamton. For eight years he headed the Medical Services of the Endicott-Johnson Medical Department in Johnson City. He was President of the Ideal Hospital Medical Staff in Endicott, 1928–32 and 1941–44.

At the time of his death, Dr. McMahon was President of the Broome County Medical Society. In the past he had served as President of the Binghamton Academy of Medicine and the Broome County Medical Bureau. Other medical affiliations included: the American Medical Association; the American Heart Association, and the Association for Study of Internal Medicine. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1934.

He did not shirk either professional committee activities or religious and civic responsibilities. At all times he was a willing and enthusiastic worker and would serve whenever called upon. The medical profession and the community deeply regret the passing of one of their ablest members.

He is survived by: Mrs. McMahon, who resides at 116 Riverside Drive, Binghamton, New York; four sons, Patrick, John, and David of Binghamton, and Ralph, Jr. of Burlington, Vermont, and three daughters, Mrs. Paul Nay, Mrs. Richard Ragard and Mrs. Doyle Bartholomew of the Triple Cities area.

JOHN H. TALBOTT, M.D., F.A.C.P., Governor for Western New York

DR. DOUGLAS DICKINSON MARTIN

Dr. Douglas Dickinson Martin, F.A.C.P., was born January 16, 1890, at Gordonsville, Virginia, and he died on May 24, 1958, of an acute myocardial infarction and coronary arteriosclerosis.

Dr. Martin graduated from the Virginia Polytechnic Institute in 1909 and from the Medical College of Virginia in 1913 with an M.D. degree. His hospital training was at Memorial Hospital in Richmond, Virginia, in 1913–14, New York Nursery and Children's Hospital in New York City in 1914, New York Lying-In Hospital in 1915 and Willard Parker Hospital, 1915–16. He had postgraduate training in naval medicine at the U. S. Naval Medical School and Internal Medicine at the University of Pennsylvania School of Medicine.

He was Chief of the Department of Pediatrics at St. Joseph's Hospital, 1935–58; an Attending Pediatrician at the Tampa Municipal Hospital, 1922–58, and Chief of the Medical Service, Pine Heath Tubercular Hospital for Children, Tampa, Florida, 1934–1938.

Dr. Martin served in the Medical Corps of the United States Navy, 1917–1921. He was a member of the American Medical Association, the Hillsborough Medical Society, the Florida Medical Association, the Southern Medical Association, a Fellow, American College of Physicians, 1931 and a Diplomate of the American Board of Pediatrics. He was a Past President of the Hillsborough County Medical Society. He was a member of the St. Andrews Episcopal Church, the Greater Tampa Chamber of Commerce, the Tampa Yacht Country Club and Ye Mystic Krewe of Gasparilla.

He wrote several articles for various medical journals.

Dr. Martin is survived by his widow, Mary Chancellor Martin; two daughters,
Mrs. Eugene Pillsbury and Mrs. John L. Dugan; a son, Douglas D. Martin, Jr. of
Tampa; three sisters, Mrs. J. C. Dickinson of Tampa, Mrs. Lutie Davenport of Richmond, Virginia, Mrs. O. W. Johnson of Lynchburg, Virginia, and three grandchildren.
To them, his colleagues in the College extend sincere sympathy and regret.

KARL HANSON, M.D., F.A.C.P., Governor for Florida

DR. ALLEN ARTHUR CLARENCE NICKEL

Dr. Allen A. C. Nickel, F.A.C.P., Bluffton, Indiana, died July 31, 1958, following an illness of four years' duration, due to heart disease. Dr. Nickel was born in Jefferson, Wisconsin, December 12, 1894.

He received his B.A. degree from North Central College, Naperville, Illinois, in 1915. An ordained minister in the Evangelical Church, he turned to the field of medicine, graduated from the University of Wisconsin (1921), and entered Rush Medical College from which he received his M.D. degree in 1923. He interned at St. Luke's Hospital, Chicago, 1923–24. From 1924–1931 Dr. Nickel was a member of the faculty of the University of Minnesota (Mayo Foundation). In 1931 he became associated with the late Dr. Charles Caylor, Dr. Harold Caylor, and Dr. Truman Caylor in the Clinic in Bluffton, Indiana. Under his guidance the Caylor-Nickel Clinic grew; it is recognized as an important medical center in northern Indiana.

Dr. Nickel was a member of the American Society of Clinical Pathologists, the Society of American Bacteriologists, the American College of Chest Physicians, the American Medical Association, and the World Medical Association. He was elected to Fellowship in the American College of Physicians in 1931.

Dr. Nickel was recognized as an outstanding and beloved citizen of Bluffton who was interested in civic affairs. He had one hobby—aviation. He owned his own plane and was for many years an enthusiast of flying.

He is survived by a daughter, Mrs. Mildred Hoffman of Detroit, and by a son, Frederick Allen Nickel, a student at Indiana University School of Medicine.

KENNETH G. KOHLSTAEDT, M.D., F.A.C.P., Governor for State of Indiana

DR. BERNARD SUTRO OPPENHEIMER

Dr. Bernard Sutro Oppenheimer, F.A.C.P., was born June 20, 1876, in New

York City and died on June 10, 1958, of multiple strokes.

Dr. Oppenheimer received his degree of Bachelor of Arts at Harvard College in 1897 and the degree of Doctor of Medicine at Columbia University College of Physicians and Surgeons in 1901. His postgraduate training included: pathology and biochemistry at the University of Berlin, in 1904–1905; cardiology at the University College Hospital Medical School, London, in 1910.

Dr. Oppenheimer's academic and hospital appointments were as follows: Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons for many years and Assistant Professor of Medicine, 1915–1936; Consulting Physician, Mount Sinai Hospital, 1940–1953; Consulting Physician, Mount Vernon Hospital, 1936–1953; Consulting Physician, Montefiore Hospital, 1933–1953; Physician, Mount Sinai Hospital, since 1927, and Montefiore Hospital, 1911–1933.

Military Service: Entered U. S. Medical Reserve Corps as Captain, 1917 and was promoted to rank of Major and Lieutenant Colonel, 1918. Subsequently Colonel until 1935. He served overseas in England and France, 1917–1918, in France as

Chief of Medical Service, U. S. Base Hospital 61, Beaune, France.

Dr. Oppenheimer was a member of the following: American Medical Association; Association of American Physicians; American Society of Clinical Investigation; Society for Experimental Biology and Medicine; Harvey Society; New York Cardiology Society and the New York Academy of Medicine. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians.

Dr. Oppenheimer was the author of many articles which appeared in the leading

medical journals.

In 1956 the Bernard Sutro Oppenheimer Fund was established by his colleagues, friends and patients. This was to be used in his name for lectures. This program is under the control of the Committee on Medical Education of the New York Academy of Medicine.

He is survived by his wife, Mrs. Enid T. Oppenheimer, 124 E. 61st Street, New York 21, N. Y. His confreres note with sincere regret the passing of Dr. Oppen-

heimer.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor, Eastern Division New York State

DR. CHARLES HERVEY SMITH

One of the oldest Fellows of the College, Dr. Charles Hervey Smith of Uniontown, Pennsylvania, died January 20, 1958, at the age of 90.

Dr. Smith was born in 1867 in the town of Dunbar, located in Fayette County, Pennsylvania. His education included study at the State Normal School of Lockhaven, Pennsylvania, and later the University of Pennsylvania School of Medicine where he was graduated with a degree of Doctor of Medicine in 1893. Dr. Smith thereafter practiced medicine in Uniontown, Pennsylvania, until his retirement in 1955.

The original Uniontown Hospital, built in 1903, owes much of its beginning to Dr. Smith. At the peak of his career, Dr. Smith enlisted in the Medical Corps of the Army during World War I where he held the rank of Major. Following the war, Dr. Smith returned to Uniontown and continued to be active there until very recently.

The records indicate that Dr. Smith was the first physician in Fayette County to be elected to the College of Physicians in the year 1921. It should also be noted that Dr. Smith began his career as a general practitioner and was one of the first in this area to limit his practice to internal medicine.

He is survived by his widow, Mrs. Elizabeth Munce Smith, 93 Morgantown St., Uniontown, Pa.

FRANK J. GREGG, M.D., F.A.C.P., Governor for Western Pennsylvania

DR. NATHAN SWERN

Dr. Nathan Swern, F.A.C.P., died suddenly of an acute coronary thrombosis on July 27, 1958. He was born in Trenton, New Jersey, on January 28, 1897, and he resided and practiced there all his life. In 1922, he received his medical degree from The Jefferson Medical College of Philadelphia. He continued postgraduate work in medicine at the Presbyterian Hospital in New York City in 1923. He pursued further training in metabolism and clinical pathology at Mt. Sinai Hospital in New York in 1925 and 1926, with additional study in metabolism in 1926 at the University of Pennsylvania Graduate School of Medicine.

Dr. Swern was Assistant in Medicine and Allergy, The Jefferson Medical College of Philadelphia, 1950-1958; and Director of the Department of Medicine at St. Francis Hospital in Trenton since 1950. He also was Director of the Radio-isotope Laboratory at St. Francis. He was a Consultant in Medicine at the Orthopedic Hospital in Trenton since 1944.

He held membership in the American Medical Association, the Medical Society of New Jersey and the Mercer County Medical Society. He also was a member of the American Academy of Allergy, the American College of Allergy and the New Jersey Allergy Society. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians (1930).

Dr. Swern led a busy and fruitful professional life. His genial and warm personality will be sorely missed by his many friends and colleagues. The sympathy of the College is extended to his wife, Mrs. Sylvia K. Swern, his only survivor.

EDWARD C. KLEIN, JR., M.D., F.A.C.P., Governor for New Jersey

DR. WILLIAM J. WALKER

Dr. William J. Walker, F.A.C.P., was born February 13, 1884, in New York City, and died on May 18, 1958, New York City, of uremia.

Dr. Walker received his degree of Bachelor of Science at the College of the City of New York, 1904, and his Doctor of Medicine degree at Cornell University

Medical College, 1908. He received his postgraduate training in Neurology and Internal Medicine at the University of Vienna, Austria, 1928; Cardiology, Mount Sinai Hospital (New York), 1933.

His hospital and academic appointments were as follows: Instructor of Physical Diagnosis, Fordham University School of Medicine, 1913–15; Instructor in Medicine (1915–20) and Assistant Professor (1920–21) at Fordham University School of Medicine. Medical Director, Fordham Hospital from 1936 until retirement; Emeritus Consultant in Medicine, Bronx Eye and Ear Infirmary.

Dr. Walker was a member of the following: American Medical Association; American Medical Association, Vienna, Austria; Medical Society of the State of New York; Bronx County Medical Society; Bronx Medical Association (Past President); Fordham Hospital Alumni Association (Past President); Fellow, American College of Physicians.

Dr. Walker is survived by two sons, Drs. Justin C. and William W. Walker, Yonkers, New York. It is with sincere regret his loss is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P., Governor, Eastern Division New York State

DR. CHARLES EDWARD WATTS

Dr. Charles Edward Watts was born in Teakean, Idaho, November 14, 1889. He died in Seattle, Washington, on October 12, 1958.

He received his Bachelor of Science degree at the University of Idaho in 1913 and his M.D. degree from Rush Medical College in 1918.

His internship year (1918-19) was spent at Cook County Hospital (Chicago). Following this he took residency training in medicine and x-ray at Washington Boulevard Hospital (Chicago) in 1919-20. He took post-graduate training in Internal Medicine at the University of Vienna, Austria. In 1920 he came to Seattle, Washington, where he established his practice and became known as one of the outstanding internists of the Pacific Northwest.

A member of the Medical Corps of the U. S. Naval Reserve since 1933, Dr. Watts attained the rank of Captain during World War II. This tour of duty included assignment as Chief of Medical Service at the U. S. Naval Hospital, Aiea Heights, Honolulu, T. H., and later the post at the U. S. Naval Hospital in Seattle.

From 1935-41 he was Lecturer at the University of Washington School of Social Work. He was the long time Chief of Medical Service at the King County Hospital in Seattle and for more than twenty years, served as Consultant to the U. S. Public Health Service Hospital in Seattle. In recent years he acted as Consultant in Medicine for the Seattle Veterans Administration Hospital. Dr. Watts was also a member of the Attending Staff of Swedish Hospital, King County Hospital and Doctors Hospital, all of Seattle.

Dr. Watts was always an active teacher of medical subjects and enjoyed a close association with the University of Washington School of Medicine ever since the inception of that institution in the mid 40's. His appointment as Clinical Professor of Medicine there dates back to 1947, and in recognition of his voluntary contribution of significant amount of time for the teaching of students, interns and residents, there has been established at the University of Washington School of Medicine, a Charles E. Watts Memorial Fund for Medical Education and Research.

He was a member of many organizations, notably the American Medical Association and the Seattle Academy of Internal Medicine. He was certified by the American Board of Internal Medicine. In addition to being a member of the following organizations, he had also been President of the Washington State Medical Association, the King County Medical Society, the North Pacific Society of Internal Medicine, the Pacific Interurban Clinical Club, and the Washington State Health Council. Dr. Watts had participated actively in the Washington State Heart Association, and had served as Vice-President of the American Heart Association.

He became a Fellow of the American College of Physicians in 1930 and served as Governor for the state of Washington from 1935 to 1942. He served as Vice-President from 1948 to 1949 and became a Life Member in 1950.

His widow, Mary Louise Watts, may be addressed at 1105 Minor Avenue, Seattle 1, Washington.

JAMES W. HAVILAND, M.D., F.A.C.P., Governor for Washington

CHICAGO CALLS!

Chicago, a great city by a great lake, is sounding its familiar convention call to members of the American College of Physicians. Responding to it during the week of April 20, will be thousands of physicians for whom attendance at the College's Fortieth Session will also be a homecoming.

At some time or other, one out of every five physicians in the United States has studied in one of the schools or hospitals of this world-renowned medical center and, consequently, this session will give him an opportunity to renew old acquaintances, revisit old haunts, and relive times past while simultaneously participating in a varied and stimulating scientific program.

Chicago is a city of superlatives—commercial colossus, industrial giant, cynosure of culture, and the greatest concentration of medical talent and facilities in the world—so it is little wonder the College will meet in the world's largest hotel, the Conrad Hilton. This vast hotel, overlooking Grant Park and Lake Michigan, will be the headquarters for the general sessions, lectures, symposia, panel discussions, color television programs, the annual convocation, banquet and exhibits.



The Conrad Hilton Hotel (Foreground) and Chicago Skyline



in the world.

It presently has 11 professional schools, including the University of Illinois College of Medicine, Stritch School of Medicine of Loyola University, and Chicago Medical School, as well as the Cook County Graduate School of Medicine. The Medical District on the city's near West Side which makes Chicago one of the leading medical centers

Hospital facilities include Cook County Hospital, the University of Illinois Research and Educational Hospitals, Presbylerian-St. Luke's Hospital, the Veterans Administration Hospital, and the Chicago State Tuberculosis Sanitarium.

The only scientific features of the Fortieth Session outside the hotel area will be the clinics presented by the Albert Merritt Billings, Cook County, Evanston, Mercy, Michael Reese, Mount Sinai, Passavant Memorial, Presbyterian-St. Luke's, University of Illinois Research and Educational, Veterans Administration (Hines), and Chicago Wesley Memorial Hospitals.



Passavant Memorial Hospital



Chicago Wesley Memorial Hospital



berculosis Sanitarium.

Presbyterian-St. Luke's Hospital



Mercy Hospital



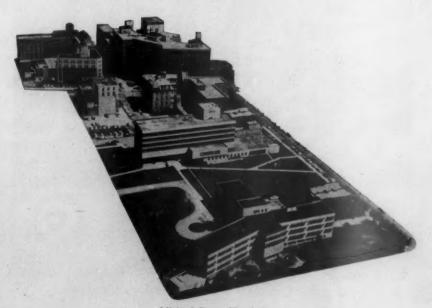
Mount Sinai Hospital



Veterans Administration Hospital, Hines, Ill.



Evanston Hospital



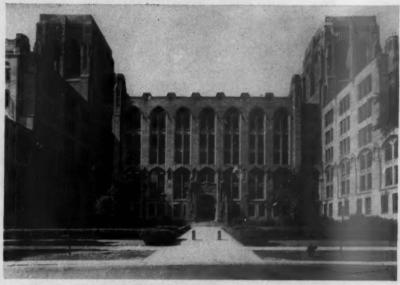
Michael Reese Hospital

The Annual Session, although one of the most comprehensive and rewarding postgraduate meetings of the year, has been programmed to allow time to enjoy a nostalgic glimpse of medical school days, for many physicians in attendance will have ties with the Chicago Medical School, or the Universities of Loyola, Chicago, Illinois, or Northwestern—or a remembrance of internship or residency at one of Chicago's great accredited hospitals.

The city's five medical schools train 2,100 undergraduate students and graduate almost 500 physicians annually, many of whom work toward their specialties in Cook County Hospital, which alone has 3,200 beds, or in one of the city's 67 other hospitals with a total bed capacity of well over 20,000.



University of Illinois College of Medicine



Albert Merritt Billings Hospital and University of Chicago School of Medicine



Chicago Medical School



Northwestern University Medical School



Stritch School of Medicine of Loyola University

Chicago is also the home of the American Medical Association, the Association of American Medical Colleges, the American College of Surgeons, the American Hospital Association, the American Dental Association, and many other specialty and voluntary health groups. Surely the medical climate of Chicago as the scene of the College's Fortieth Annual Session could not be more conducive to the work at hand.

Yet it will not be all work! Those who attended the previous session in Chicago will recall the outstanding concert by the Chicago Symphony Orchestra, and they will be delighted to know that as one of America's three greatest assemblages of musicians, under the baton of Fritz Reizer, the orchestra will again present a concert for the College members and their guests.

Other social highlights, of especial interest to the distaff, will be teas, tours, and style shows. And just shopping on the "Magnificent Mile" of Michigan Avenue, in the famed department stores of State Street, and in the chic shops of the near north Gold Coast area, is reason enough to have your ladies join you in Chicago.

What else? April is synonymous with baseball, and the White Sox and the Cubs will be back from hibernation. The racetracks are open, the theatre marquees are ablaze, and the nightclubs never close. For the children, Chicago is a veritable playground with its beautiful parks, lakefront, forest preserves, zoos, museums, aquarium, observatory, and skyscraping views.

Chicago entertains millions of guests each year—so it knows how to do it well. For all these reasons, the American College of Physicians is delighted to return to Chicago once again for its Annual Session. The convention call is sounding . . . so make a date April 20-24 for that great city by a great lake—CHICAGO!

ELIOT E. FOLTZ, M.D., F.A.C.P.

Metamucil[®] does BOTH!

In constipation, Metamucil produces SOFT, easy stools and activates gentle peristalsis. By adsorbing and retaining water within the stool Metamucil prevents hard feces from forming. And it adds to intestinal residue a soft, plastic bulk which ACTIVATES the normal reflex activity of peristalsis.

Metamucil is a brand of psyllium hydrophilic mucilloid with dextrose.

SEIRLE

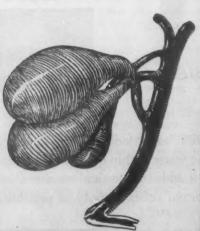
AN AMES CLINIQUICK

CLINICAL BRIEFS FOR MODERN PRACTICE

HOW PREVALENT ARE MULTIPLE GALLBLADDER ANOMALIES?

One hundred and twenty-two cases of vesica fellea divisa (bilobed gall-bladder) and vesica fellea duplex (double gallbladder with 2 cystic ducts) are reported in the literature. A unique case of vesica fellea triplex has recently been described.

Source: Skilboe, B.: Am. J. Clin. Path. 30:252, 1958.



in medical management and postoperative care of biliary disorders...

"effective" hydrocholeresis . . .

DECHOLIN°

(dehydrocholic acid, AMES)

"...dehydrocholic acid...does considerably increase the volume output of a bile of relatively high water content and low viscosity. This drug is therefore a good 'flusher,' and is effectively used in treating both the chronic unoperated patient and the patient who has a T-tube drainage of an infected common bile duct."

free-flowing bile
plus reliable spasmolysis

DECHOLIN® WITH BELLADONNA

"...DECHOLIN/Belladonna in a dosage of one tablet t.i.d. for a period of two to three months may prove helpful in relieving postoperative symptoms, aiding the digestion, and facilitating elimination."²

(1) Beckman, H.: Druga: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 425. (2) Billiary Tract Diseases, M. Times 85:1081, 1957.



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THE HEART DISEASE PATIENT NEEDS RELIEF FROM

STRESS



ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease." (Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

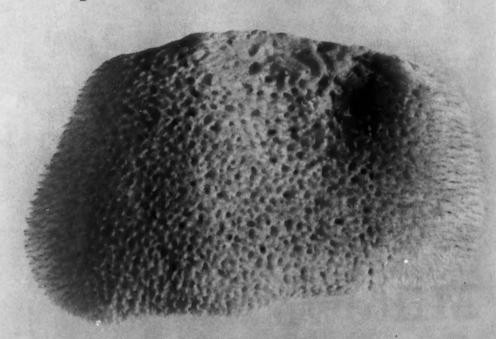
menrohamate (Wallace)

Available in 400 mg. scored and 200 mg. sugarcoated tablets. Also available as MEPROSPAN* (200 mg. meprobamate continuous release capsules). In combination with a nitrate, for angina pectoris: MILTRATE*-(Miltown 200 mg. + PETN 10 mg.). TRADE-MARK

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, New Brunswick, N. J.

How a new principle creates round-the-clock therapy for the peptic ulcer patient



What are the important needs of treatment in peptic ulcer?

Dietary reform, certainly; some discreet counseling. And for the symptoms themselves, a good anticholinergic. To this end, Abbott produced TRAL—an anticholinergic of unusually high selectivity.

What then?

The convenience—or, rather the inconvenience—of the peptic ulcer regime becomes a consideration. Important? This, of course, depends on the individual patient—severity of his symptoms, his dosage needs, his temperament, his personal capacity to conform faithfully to the regime.

Clearly, long-acting medication may be of help.

Various methods for prolonging drug action are available to the physician. Some work better than others. But the gastrointestinal system—especially one that is ailing—is not so cooperative as we would like. Long-acting tablets and capsules have a hard time of it, because they often function better at one pH than at another . . . or depend on an ideal motility rate . . . or release their drugs too slow or too fast when enzymatic activity changes.

Abbott has by-passed these problems. Abbott offers a long-acting dosage form that releases its drug smoothly, slowly, independently of digestive function. It is the Gradumet.

Structurally, the GRADUMET is rather like the sponge. An inert, porous matrix, it is honeycombed with thousands of tiny passageways. TRAL fills these passageways. As the GRADUMET makes its winding trip through the g.i. tract, it releases its TRAL by a leaching action—a therapeutic amount at first, a maintenance dose over the ensuing 8 to 12 hours. The exhausted GRADUMET is excreted harmlessly, later.

The result: Continuous anticholinergic therapy all through the day—or the night—from a single oral dose.

Just one thing: If you prefer the long-acting form of TRAL, be sure to specify TRAL GRADUMET. (The drug is supplied in Filmtab® form, too.)

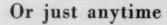
New Tral Gradumet, 50 mg., and Tral Gradumet, 50 mg. with Phenobarbital, 30 mg., are both available at all pharmacies, in bottles of 50 and 500.

TRAL Gradumet®

(HEXOCYCLIUM METHYLSULFATE IN LONG-RELEASE DOSE FORM®, ABBOTT

for F.A.C.P.'s only.

Holidays . . Birthdays . . Anniversaries . . .





FELLOWSHIP INSIGNIA FOR ACADEMIC GOWN

The insignia for academic dress consist of a cross in the shape of the Fellowship Key, exact size as illustrated, of green velvet with the Seal of the College outlined in solid gold braid, to be worn at the option of the Fellow on the right sleeve of the academic gown, about three inches below the shoulder seam. These insignia are made up on order ready to be stitched to the gown.

Price, delivered, \$7.00.

FELLOWSHIP TIE CLASP



This distinctive tie clasp meets the need of those who have no use for a Fellowship Key because they do not wear a watch chain. The College emblem is wrought in solid gold; the bar is gold filled in good and lasting quality.

Price, including tax, delivered, \$12.00.



FELLOWSHIP KEY

This beautifully and expertly designed charm, bearing the Seal of the College, is wrought in 10K solid gold and embossed in the College colors. Shown actual size. Initials of Fellow and date of election engraved on the back at no extra charge.

Price, including tax, delivered, \$12.00.

Available also, in smaller size, as a Fraternity Pin with Safety Catch, \$5.00.

The American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

Dear Sir:

Please send me:

Fellowship Insignia for Academic Gown \$ 7.00 \$...

Fellowship Key 12.00 \$...

Fellowship Pin 5.00 \$...

Fellowship Tie Clasp 12.00 \$...

My check for \$... is enclosed. Total \$...

Name (Please Print)

Street City Zone State

Amsterdam, Bernard: New York J. Med. 58:2199-2212 (July 1) 1958.

Panel Discussion on Proper Nutrition for the Older Age Group, J. Am. Geriatrics Soc. 6:787-802 (Nov.) 1958.

Leckert, J. T.; Donovan, C. B.; McHardy, G., and Cradic, H. E.: J. Louisiana M. Soc. 110:260-266 (Aug.) 1958.

blood cholesterol regulation is worth while . .

Arcofac lowers blood cholesterol levels. The Arcofac regimen is safe...well tolerated... effective... and imposes no radical changes in diet.

Arcofac supplies linoleic acid, an essential polyunsaturated fatty acid that lowers high blood cholesterol levels. It also provides vitamin B₀ which is deemed necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Vitamin E, a powerful antioxidant, helps maintain the fatty acid in an unsaturated state.





Armour Cholesterol Lowering Factor

Each tablespoonful of Arcofac contains:

Pyridoxine hydrochloride......1.0 mg. (Vitamin B_d)

†Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.

*Added as mixed Tocopherois Concentrate, N.F.

Exactly how

does new Halodrin* restore the "premenopausal prime" in postmenopausal women?

Webster defines "prime" as the period of greatest health, strength, and beauty. In a woman, these are the childbearing years between puberty and menopause—the years when her hormone production is highest.

The inevitable reduction in this hormone production as she enters the menopause often results in physical discomfort in the form of hot flushes, nervousness, insomnia, or a multiplicity of other symptoms with which you are familiar. Superimposed on this physical picture is the psychic trauma brought on by this unavoidable evidence of aging. The thing that brings her to a physician is simply that she "feels bad."

You can't make her 35 again—but the odds are good that you can make her feel like it! The secret is a combination of reassurance and hormones. The exact form and amount of the former defy objective analysis, but the latter can now be provided with scientific precision. Reduced to essentials, here is the explanation of exactly how hormones—in the form of Upjohn's new Halodrin—restore the "premenopausal prime."

The normal premenopausal woman secretes estrogens in the urine in the form of estradiol, estrone, and estriol, in an approximate 28-day average ratio of 39:15:46. Starting with this urinary excretion of estrogens, it is possible to calculate backwards and estimate the amount of estradiol that must have been secreted endogenously in order to produce these urinary levels. This is possible because the proportion of estrogens which appears in the urine following parenteral administration has been established in castrated women.

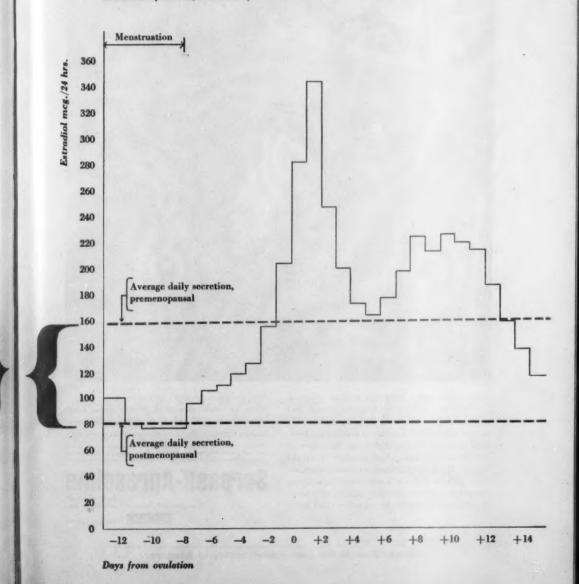
On this basis, the average endogenous output of estrogens is about 160 micrograms per day during a menstrual cycle, and 80 micrograms per day in postmenopausal women (see chart opposite). Therefore, the restoration of the "premenopausal prime" in the postmenopausal woman requires the replacement of approximately the equivalent of the 80 micrograms of estradiol per day that she no longer secretes endogenously.

Oral ethinyl estradiol is about 2 to 2½ times as potent as parenteral estradiol. Therefore, the replacement of 80 micrograms of endogenous estradiol production per day is accomplished by the oral administration of 32 to 40 micrograms of ethinyl estradiol per day.

Each Halodrin tablet contains 20 micrograms of ethinyl estradiol, which means that the recommended dosage of 2 tablets per day provides 40 micrograms of ethinyl estradiol. This offsets the loss of 80 micrograms of endogenous estradiol production in the menopausal woman; i.e., restores the "premenopausal prime."

Each Halodrin tablet also contains 1 mg. of Upjohn-developed Halotestin* (fluoxymesterone)—the most potent oral androgen known. The primary purpose is to "buffer" the ethinyl estradiol just enough to prevent breakthrough bleeding, which is obviously undesirable in the menopause. It also exerts other beneficial hormonal effects, one of which, in common with ethinyl estradiol, is a powerful anabolic action so desirable in patients of advanced years.

Endogenous estrogen secretion (mcg./24 hours) (calculated from average 24-hour urinary excretion of estradiol, estrone, and estriol)



WHEN BLOOD PRESSURE MUST COME DOWN...



When hypertensive symptoms such as dizziness, headache and fainting are frequent enough and severe enough to interfere with your patient's activity and safety—then it is time to consider the beneficial actions of Serpasil-Apresoline. Both Serpasil and Apresoline lower blood pressure. When the Serpasil-Apresoline combination tablet is prescribed, blood pressure response is even better. In addition, Serpasil contributes favorable calming and heartslowing effects. Apresoline increases renal blood

flow, decreases cerebral vascular resistance and inhibits the actions of humoral pressor agents. Combined with Serpasil, Apresoline is effective at a lower dosage, thus side effects are rarely a serious problem.

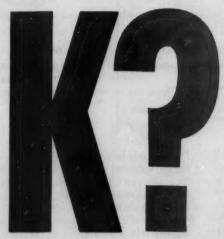
supplies. Tablets #2 (standard-strength), each containing 0.2 mg, of Serpaili and 50 mg, of Aprecoline. Tablets #2 (half-strength), each containing 0.2 mg, of Servasil and as mg, of Aprecoline. Supplies maintainly on consect

Serpasil'-Apresoline

hydrochloride erpine and hydralazine hydrochloride CIBA)

SUMMIT, NEW JERSEY

why all the fuss over potassium?



Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because

clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.



"FC buil

IS THIS YOUR PATIENT?



EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue Posture is poor

No x-ray evidence of bone lesions

2.



LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain") Patient is round shouldered, walks with a stoop

X-ray reveals compression fractures of lower vertebrae

3.



70 AND OVER

Fracture of hip after a minor fall X-ray reveals fracture of neck of femur X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of low back pain, vague aches and fatigue may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as wrinkled and thinning skin, a tendency to appear older than stated years; there may also be hypercalciuria when postmenopausal osteoporosis is complicated by acute osteoporosis of dieuse

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteo-blastic activity or retards the formation of protein and connective tissue such as prolonged immobilization, contisone therapy, or malnutrition will favor development of osteoporosis in both male and female.

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"FORMATRIX" contains three most essential bone building materials necessary for matrix formation, estrogen, androgen and vitamin C.

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EARLY POSTMENOPAUSE No x-ray evidence of bone lesion

2.



LATER POSTMENOPAUSE

X-ray reveals compression fracture of lower vertebrae

3.



70 AND OVER

X-ray reveals fracture of neck of femur

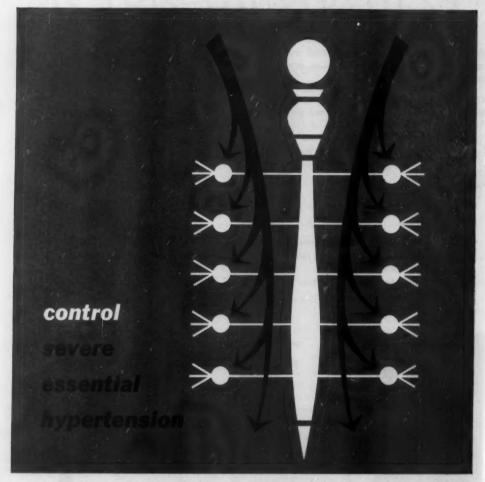
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in osteoporosis

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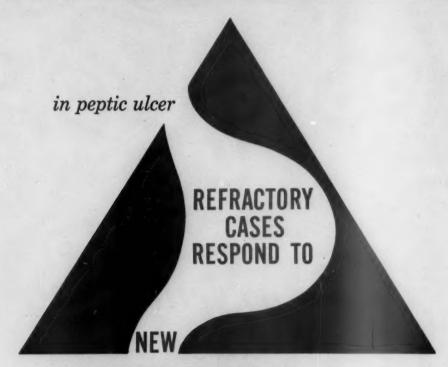
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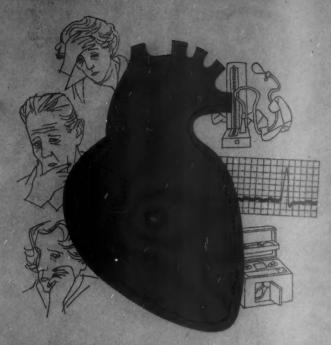


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J. Eskwith, I. S.: The holistic approach to angine pectoris. Am. Heart J. 55:621, April 1958.



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Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) 46:493 (Aug.) 1957.
 Barr, M., and Arnista, E.S.: *Ibid.* 46:486 (Aug.) 1957.
 Barr, M.: *Ibid.* 46:490 (Aug.) 1957.

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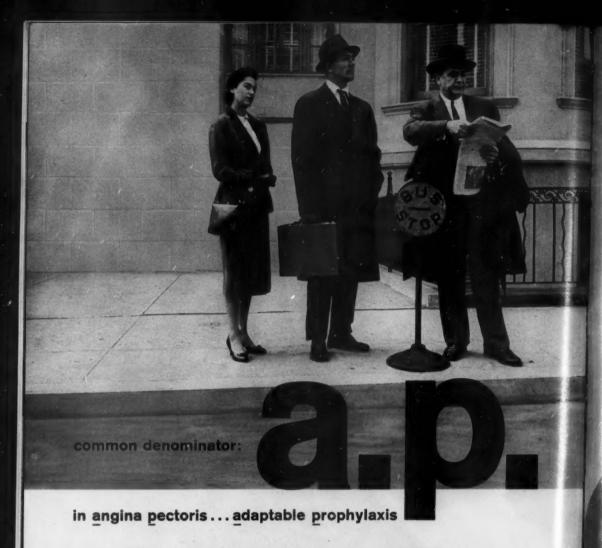
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Cass, L.J., et al., J.A.M.A. 168:1829 (April 12) 1958.
 Batterman, R.G., et al., Am. J. M. Sc. 234:413 (Oct.) 1957.
 Medical Department. Wyeth: Final Report on the Clinical Evaluation of Zactirin.



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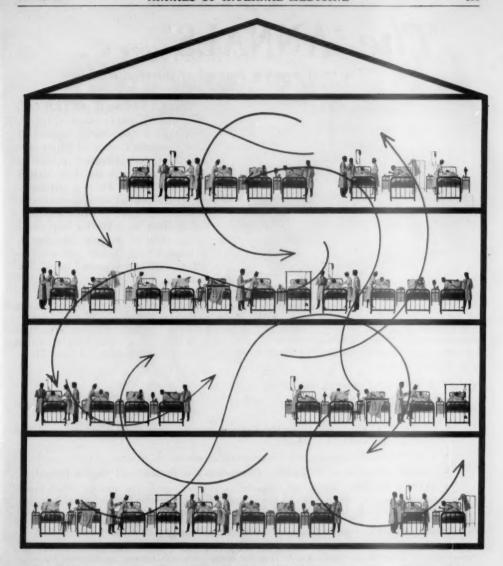
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1. Phillips, R. E.: Am. Pract. & Digest Treat. 7:1573, Oct. 1956. 2. Selling, L. S.: J.A.M.A. 157:1594, April 30, 1955. 3. Altschul, A. and Billow, B.: New York J. Med. 57:2361, July 15, 1957. 4. Ross, S. T.: Postgrad. Med. 23:24, Jan. 1958. 5. Tacket, H. S.: Am. Pract. & Digest Treat. 8:597, April 1957. 6. Bodi, T., Wirts, C. W., Jr. and Menduke, H.: Am. J. Gastroenterol. 29:643, June 1958.

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Smith et al.4	109	75	3	3	28
Fitzpatrick et al. ⁵	120	61	5		54
Lerner ⁶	30	20	4	1	5
	309	188	15	4	102

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- 1. Reports to the Squibb Institute for Medical Research.
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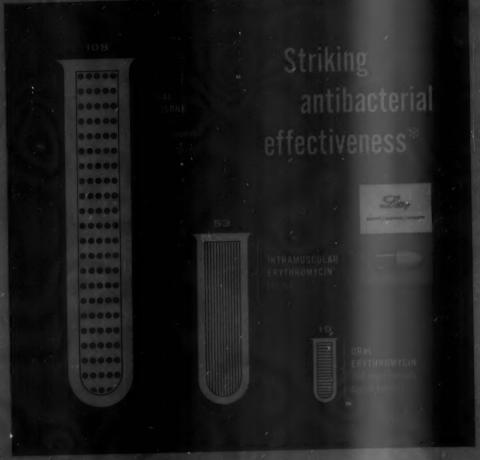
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